Nutrition and Health
Series Editor: Adrianne Bendich

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Sherma Zibadi *Editors*

Nutrition in Infancy

Volume 2

Humana Press

Nutrition and Health Series

Adrianne Bendich, PhD, FASN, FACN, Series Editor

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Preface

For millennia the importance is known to mothers and critical for child growth and survival. With the expansion of biomedical research in the late twentieth century fine details and specific solutions to prevention and treatment of childhood growth, diseases, and health can be defined. The editors have decades of research and interest in nutrition and health including editing a previous version of Nutrition and Infancy a dozen years ago. With many advances in studies on the role of foods and nutrients in childhood necessitated an updated version with expanded authors and topics in seven major areas as part of a *two volume set*.

Volume 1

Overview: global perspectives. This section begins with discussions of infant nutrition and lifelong health including adverse effects on infants in the Middle East and aboriginals in Canada. Developing problems for infants are reviewed on the role of fatty acids on neurological development and obesity.

Premature infant feeding. This section has six sections focusing on nutrition and premature infant health. These range from protein supplementation, colostrums, and total parenteral nutrition. Importantly these therapies effects on growth as well as defining knowledge and research gaps are discussed.

Breast feeding: growth and health. This historical and traditional method of infant feeding makes up one of two major sections of the book with nine diverse reviews. Breast milk has major roles in growth, development, obesity, and body composition. The causes and solutions to early breast milk feeding cessation. Thus the need to store breast milk and maintain their functions is critical to many mothers. Breast feeding in special populations including the Indian subcontinent vary. A variety of factors affect breast milk including maternal dietary salt, diet, milk oligosaccharides, and tobacco smoking are discussed to thereby modifying infant health. The question of breast milk and risk of subsequent breast cancer is reviewed. Importantly methods to improve use of breast feeding and its duration on infant growth and health are defined.

Micronutrients and healthy infant nutritional status. Clearly maternal supplement has been used to have effects on infants and benefits/risks are reviewed along with food fortification. Importantly the role of nutritional support of children with inborn errors of metabolism will be very helpful to physicians. Finally major vitamins are reviewed including vitamin A status assessment and role in health, vitamin K deficiency, and micronutrient deficiencies in infant skin problems. Magnesium is developing as a new mineral to use in infant health as described in its chapter.

Volume 2

Nutrition and neonatal/infant disease. Nutrition in infant diets plays key role in treatment of various challenging diseases and form the second major section with eight reviews. For examples, the reviews of intractable epileptic, chronic diseases, liver disease, short bowel syndromes, and Crohn's disease show important roles of diet to manage and treat them. Nutrition and diet supplement are reviewed as modulators of undernutrition-induced hearing loss, diabetes, and HIV-induced malnutrition. Hormones as therapy affect beneficially infants with kidney disease. Glangliosides are modified by diet affecting neurological development. The role of dietary supplementation in developmental or genetic disease like celiac disease, acute gastroenteritis, and intestinal failure are reviewed. Surgery is sometimes needed to correct birth issues and an example is reviewed, percutaneous endoscopic gastrostomy designed for children. In support of surgeries in infants the role of nutrition for those undergoing it is defined. Many diseases of infants have a nutritional component or therapy.

GI tract considerations. Parental nutrition can play important roles in the growth and development of the gastrointestinal tract of infants that need supplementation. This can include home parenteral nutrition in developing countries or low-income families. Colonic flora respond to diets and supplements and affect the infants' growth and development. Thus pro and probiotics are reviewed as potential over-the-counter prevention and therapies to treat disease and promote growth.

Formulas in health and disease of infants. Historically formulas with food and nutrition components have been used as therapies by physicians. Home and hospital parenteral nutrition are reviewed in two chapters. Two other chapters review parenteral nutrition in premature infants and promotion of safety in disease prevention. Parenteral nutrition is the major focus of this section. Probiotics and probiotics are novel and developing for disease therapy and promotion of infant growth. Protein nutrition is key for helping undernourished preterm infants.

Hormones and lipids: growth and development of infants. Hormones and lipids are becoming applied in diets, therapies, and from mother's milk to affect infants. Diet's role in managing hypercholesterolemia is defined. The role of infant adipose tissues and its hormones in changing infant development are carefully and completely reviewed. Maternal behavior and diet affect the infant as defined by clinicians in a review. Finally hormone therapy is described as it improves growth in infants with chronic kidney disease.

Summary. A wide range of nutritional and food-related therapies to prevent or ameliorate disease, growth retardation, and promote health are outlined by 113 experts in 59 chapters. This book becomes a definitive source for much of the methods and approaches to use nutrition to promote well-being in infants.

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Series Editor

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes: 1) a synthesis of the state of the science, 2) timely, in-depth reviews by the leading researchers in their respective fields, 3) extensive, up-to-date fully annotated reference lists, 4) a detailed index, 5) relevant tables and figures, 6) identification of paradigm shifts and the consequences, 7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, 8) suggestions of areas for future research and 9) balanced, data-driven answers to patient as well as health professionals questions which are based upon the totality of evidence rather than the findings of any single study.

The Series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The editor(s), whose training(s) is (are) both research and practice oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

"Nutrition in Infancy", edited by Professor Ronald Ross Watson, PhD, Professor George Grimble, PhD, Professor Victor R. Preedy, PhD, DSc, FRIPH, FRSH, FIBiol, FRCPath and Dr. Sherma Zibadi, MD, PhD clearly exemplifies the goals of the Nutrition and Health Series. The major objective of this comprehensive two volume text is to review the growing evidence that nutrition provided in utero and during infancy directly affects the entire lifetime health of the individual. This volume includes 60 up-to-date informative reviews of the current major dietary issues. Practicing health professionals, researchers and academicians can rely on the chapters in this volume for objective data-driven sources about essential vitamins and minerals, proteins, fats, and carbohydrates. This new comprehensive review of the science behind the nutritional strategies to assure the health of the neonate is of great importance to the nutrition community as well as for health professionals who have to answer patient, client or graduate student questions about the newest clinical research in nutrition and infancy.

"Nutrition in Infancy" represents the most comprehensive compilation of the recent data on the actions of specific essential nutrients and bioactive dietary components on fetal development and growth of the preterm and term infant. It is to the credit of Drs. Watson, Grimble, Preedy and Zibadi that they have organized this volume so that it provides an in-depth overview of the critical issues involved in the determination of the best nutrition for infants including those born preterm, those with medical conditions that require specific dietary interventions, those born in developing nations or in developed nations, those with special GI tract requirements and those with genetic factors that affect the metabolism of certain foods and/or nutrients.

Each of the two volumes contains about 30 comprehensive chapters. The first volume contains four related sections. The first section, an overview of global perspectives on infant feeding practices, contains seven chapters that include reviews of the history of breast feeding from the beginning of time up until present times; there are several unique chapters that describe the discovery of the infant requirements for vitamins and government projects to assure the nutritional adequacy of infant feeding programs. This is especially important when populations may be far from medical resources such as described in the chapters discussing infant nutrition issues in Aboriginal children living in remote regions such as in Northern Canada; infants from India, Pakistan, and Bangladesh; Middle East and North Africa. Infants can triple their birth weight during the first year of life and the quantity as well as the nutritional quality of the diet can affect the growth rate dramatically. The introduction of complementary foods during infancy in developing countries is usually dependent upon cultural norms and these are outlined for a number of African and East Asian nations in the next chapter. The final chapter in this section includes a synthesis of studies examining the potential for development of food allergies in children from developed countries. The chapter provides valuable discussions and tabulates the data on the importance of timing of introduction of specific foods to infants and subsequent development of asthma and/or allergies.

The second section contains six chapters on premature infant feeding. The chapter authors remind us that fetuses increase their weight 10 fold in the second and third trimester with concomitant gains in height and head circumference. Preterm birth may therefore result in stunted growth due to a variety of medical conditions. There is an important discussion of accurately determining whether a preterm neonate is small for its gestational age or growth retarded. If the birth weight is less than the 10th percentile-for-gestational age, this is defined as small-for-gestational age (SGA). Growth restriction and constitutional slow growth represent two distinct processes independent of SGA and are associated with different potential adverse outcomes. Potential maternal factors linked to preterm birth are reviewed in several chapters. These include smoking, gestational diabetes, infections, malnutrition, preeclampsia and most recently, excessive maternal weight as well as excessive maternal weight gain during pregnancy.

Preterm infants usually lose more weight after birth than term infants. Preterm infants require greater protein and lipid administration following birth and increased vitamin, mineral and caloric supplementation throughout the first year of life. The absorption and bioavailability of nutrients by the premature gut differs from that of the fetus that obtains nutrients across the placenta. The significant medical morbidities seen in preterm infants especially lung disease that requires ventilation and/or serious infections that require targeted nutritional interventions, add to the nutritional stresses seen in the preterm infant. The development of the microbiome also differs in preterm infants compared to term infants due to gut immaturity and medical conditions as mentioned above. Even when preterm infants reach term equivalent, their pattern of growth continues to differ from infants born at term. Thus, these chapters provide detailed information on methods used to evaluate growth and nutritional status in preterm infants.

One of the major considerations of preterm morbidity is that preterm infants exhibit intestinal wall immaturity which is measured as increased intestinal permeability. The importance of human breast milk and other sources of nutrients for the premature infant are discussed in a single detailed chapter. The authors discuss the fact that the gastrointestinal (GI) system doubles in length from 25 to 40 weeks' gestation. Preterm birth significantly increases the risk of necrotizing enterocolitis, an inflammatory cascade that leads to ischemia/necrosis of the intestines. This disease is found in 7-10% of very low birth weight infants who are usually born before the 25th week of gestation and is associated with 33% mortality and 33% long-term GI and/or neurodevelopmental morbidity. Several chapters review the data concerning the importance of glutamine and arginine in reducing gut permeability. Related to GI tract maturation is the availability of maternal colostrum. The chapter on colostrum reviews the immunological as well as nutritional importance of this first milk especially to very low birth weight preterm infants. Another important nutrient for the preterm infant is protein. Unlike term infants who have a recommended daily protein intake of 1.5 g/kg/day for the first 6 months of life, the

smallest preterm infant can have an increased protein need of about 4 g/kg/day and preterm infants >750-1500 grams require at least 3-3.5 g/kg/ day depending upon their medical conditions.

The preterm infant's protein requirements from parenteral and enteral sources are discussed in detail in the next two chapters. The chapters review the importance of parenteral nutrition (PN) for preterm infants. The provision of nutrients intravenously is complicated in adults, and it is extremely complicated in the smallest, least developed preterm infants. Not only are the procedures complex, but the administration of the correct balance of nutrients, fluids and maintenance of non-infective complications is of paramount importance. The determination of standards of growth for the preterm infant given parenteral nutrition is ongoing and several important studies are reviewed and extensively tabulated for the reader. These detailed chapters provide practice-based suggestions concerning the most critical aspects of assuring the health of the preterm receiving PN during the first days of life.

Nine chapters examine the role of breastfeeding in the growth and health of the term infant. The third section includes reviews of the nutritional value of human breast milk and the consequences of maternal smoking on these nutrients. There are also unique chapters on methods to improve the initiation and success of breastfeeding, another on potential reasons why infants stop breastfeeding and potential ways to restart breastfeeding; a chapter that reviews the totality of the evidence concerning the association of breastfeeding and cancer risks in the breastfed child, and a chapter on storage of breast milk with protocols tabulated for the reader. The section begins with a chapter on human milk oligosaccharides (HMO), complex carbohydrates abundant in human milk. Recent data show that HMO might protect very-low-birth-weight preterm infants from necrotizing enterocolitis. HMO help establish and maintain a healthy colonic microbiome. The authors remind us that currently there are no human clinical research studies with HMO.

The next chapter updates information concerning the role of breastfeeding duration and lowered risk of childhood and adult obesity. The authors objectively review the recent meta-analyses and also examine the data from studies with formula-fed infants. Maternal dietary factors that can affect breastfeeding duration are discussed in the chapter that describes the role of maternal dietary salt intake. Factors including maternal diabetes, obesity and undernutrition are examined in detail. Maternal smoking and/or fetal exposure to environmental tobacco smoke and its effects on the neonatal immune and respiratory systems is reviewed in the next chapter. There is a strong association between smoking exposure and increased risk of asthma and allergies in the neonate and the child of smoking parents. Moreover, maternal smoking is associated with reductions in oxytocin that is required for release of milk from the breast.

The fourth section, entitled "Micronutrients and Healthy Infant Nutritional Status", contains nine chapters that include examination of foods as well as individual nutrients. The prevalence of micronutrient deficiencies in infancy and in the second and third years of life are reviewed in the first chapter. Reference values from the World Health Organization are tabulated. Provision of supplements to expectant mothers is one strategy proposed to reduce infant nutritional deficiencies especially in developing countries. Supplemental iron, folic acid, calcium, zinc, vitamin D, vitamin A and other essential nutrients are discussed. Another strategy is food fortification that has the benefit of not having to change dietary habits. Successful fortification programs including iodization of salt, addition of iron and folic acid to staple foods and addition of vitamin A to rice are reviewed in detail.

The importance of examining the amino acid and protein sources and content of infant formulas is reviewed in the next chapter that reminds the reader that cow's milk and human milk differ significantly in their major proteins as well as the protein's amino acid concentrations. The potential consequences of these differences are discussed in light of the differences in compositions between currently available formulas. Taurine is considered a non-essential amino acid in adults, but may be essential to the developing embryo, fetus and neonate. The value of taurine for optimal development of the cardiovascular system is discussed in a separate, well-illustrated chapter. There is an additional chapter that reviews the importance of gangliosides in neuronal development and the value of placental transfer and human breast milk as sources of gangliosides for the developing fetal and infant brain and nervous systems.

Determination of micronutrient deficiencies in infants, especially in developing countries where medical facilities may not be nearby, is of great importance as these are often multi-micronutrient deficiencies that can result in serious adverse effects. The chapter describing the cutaneous and mucous membrane manifestations of nutritional deficiencies reviews the symptoms that can be seen during the early stages as well as later deficiency diseases. In addition, treatment modalities for the most commonly seen vitamin and mineral deficiencies are described. One of the micronutrient deficiencies that may be overlooked is magnesium deficiency. The chapter on magnesium tabulates the requirements for this mineral in infants and young children, manifestations of low as well as high magnesium status and the consequences of these conditions in infants. Vitamin K is another essential micronutrient that may be low in the term infant and is often in very low concentrations in the blood of preterm infants. Vitamin K is essential for the synthesis of certain coagulation factors. If the neonate's plasma concentration of vitamin K is low, they may suffer from vitamin K deficiency bleeding, previously called hemorrhagic disease of the newborn. In the developed nations, neonates are supplemented with vitamin K immediately after birth. As described in the next chapter, neonates, and particularly those who are breastfed, benefit from prophylactic vitamin K but cost implications may be prohibitive in some regions of the world. The final chapter in this section reviews the importance of optimal vitamin A status in the mother and infant as a key determinant in maintaining the infant's natural immunity. Also included in the chapter is a discussion of the weaning transition time and diet as weaning is a risk factor for vitamin A deficiency. One strategy may be to improve maternal vitamin A status and her breast milk vitamin A levels so that the infant can build sufficient body reserves of vitamin A prior to the transition. Improving vitamin A content in weaning foods is also important.

The second volume of "Nutrition in Infancy" emphasizes clinical conditions found in infancy. Half of the second volume is devoted to reviews of the clinical significance of nutritional factors in infants with diseases and/or conditions that are either inherited or develop postnatally. Section E contains 17 chapters devoted to these critical practice- related topics. The first chapter in this section describes two examples of altered body composition in children; those with cerebral palsy and Down syndrome, both prevalent disorders with differing etiologies, but significant and opposite impacts on growth, body composition and nutritional status. These differences require separate approaches for accurate nutrition-related clinical assessment and management that are described in detail. The second chapter provides an extensive overview of the major nutritional consequences and treatments of inborn errors of metabolism. Conditions reviewed include amino acid genetic errors such as phenylketonuria, errors in carbohydrate metabolism resulting in glycogen storage diseases and errors in fat metabolism. The third chapter on epilepsy in infancy reviews the importance of the ketogenic diet which is a high fat, low carbohydrate diet with an adequate amount of protein that mimics the metabolic state of fasting during an anabolic situation. This special dietary regime is used in conjunction with anti-epileptic drugs and also when the drugs do not provide benefit to the infant or young child. The chapter includes detailed appendices and tables.

Seven of the 17 chapters examine serious acute as well as chronic gastrointestinal (GI) diseases. There is a unique chapter that describes the effects of inherited malformations in the cranium and/or oral cavity on the nutritional status of the infant and growing child. Also included in this chapter are discussions of maintenance of the early teeth and avoidance of caries. Even when cranio-facial development is normal, feeding difficulties can arise in the neonatal period due to biological, developmental or behavioral issues. Reduced efficiency in feeding often occurs when there is oral motor dysfunction, which is common in children with developmental disabilities. With regard to acute gastroenteritis, this is the commonest indication seen in children in emergency rooms in the US. Diarrhea, usually caused by viral infection, is reviewed in detail and provides current treatment methods depending upon laboratory findings, diagnosis and current nutritional status of the child. The detailed description of the physiology of the gastrointestinal tract provides excellent background information for understanding the effects of pathological conditions discussed in subsequent chapters. Over 20 pathogenic conditions are described in detail including viral, bacterial and parasitic infections.

As described in the chapter on short bowel syndrome, intestinal failure is defined as the critical reduction of functional gut mass below the amount that is minimally necessary for adequate digestion and absorption to satisfy nutrient and fluid requirements for growth in children. Therefore the use of parenteral nutrition (PN) is required. Intestinal failure may result from intestinal obstruction, dysmotility, surgical resection, congenital defects, or disease-associated loss of absorption. Intestinal failure may be caused by short bowel syndrome (SBS), mucosal enteropathy, or dysmotility syndromes. SBS is a subcategory of intestinal failure, which may result from surgical resection, congenital defect or disease-associated loss of absorption. This condition is characterized by the inability to maintain protein-energy, fluid, electrolyte or micronutrient balances when on a conventionally accepted, normal diet. One of the mechanisms used to provide nutrition to the infant with serious gastrointestinal issues is the use of a gastric feeding tube (gastrostomy). The next chapter describes this procedure, its benefits and risks. The commonest reason for gastrostomy placement in children is neurological disability, either congenital or acquired brain injury; other causes include congenital heart disease, chronic lung disease, cystic fibrosis, congenital malformations that prevent swallowing and malignancy.

The chapters that review Crohn's disease, celiac disease, intestinal failure, acute and chronic gastroenteritis and liver diseases also contain clinically relevant discussions of signs and symptoms and current therapies including considerations of use of enteral as well as PN where warranted. The chapters include excellent tables and figures as well as guidelines for patient evaluations of macro and micronutrient levels that are often affected by these chronic disease states that often develop in infancy, during the transition to semi-solid foods from breast feeding, and/or in early childhood. Relevant data on occurrences in developed and developing nations are included. As there are many commonalities between the symptoms seen in these chronic conditions, including failure to thrive, diarrhea and stunting, each chapter author provides specific mechanisms available to determine the exact causes of the gastric distress.

The final five chapters in this section examine the nutritional effects of kidney disease, HIV infection and diabetes. The chapters on the effects of undernutrition on hearing capacity, and the ability to fight infections that may be associated with surgery in infancy complete this section. The common thread of potentially severe malnutrition associated with these conditions is reviewed with emphasis on clinically validated methods to overcome growth retardation and improve GI functions. Specifically, in the chapter on HIV infection, the WHO guidelines are included as well as tabulation of the clinical studies in HIV-infected mothers and multifactorial effects of breastfeeding. Another unique chapter describes the fetal development of hearing and reviews the anatomy and physiology of the auditory processes. The chapter examines the micronutrients most commonly associated directly or indirectly with hearing impairment including iodine, iron, zinc and vitamins A, B12 and D. The chapter on Type I and Type II diabetes reminds us that this is the most common metabolic disease in infants and children. Nutritional management during early childhood is described in detail. The final chapter in this clinically-focused section examines the effects of severe stresses on the infant that include events such as cardiac surgery and burns. Young children, due to their low protein reserves, are particularly vulnerable to the adverse nutritional effects of stress. The chapter reviews the role of nutrition support in helping to preserve skeletal muscle and support organ and immune function. The optimal levels of macronutrients, micronutrients, energy and nutrition support in critically ill children are unknown. Predictive equations may not adequately predict energy needs during critical illness. As all of the authors acknowledge, more research in the area of nutrition support for the acute and/or chronically ill child is urgently needed.

The sixth section contains five chapters that examine PN in detail as well as the importance of the microbiome in the infant, toddler and growing child. The two comprehensive chapters that describe PN in the hospital and home settings provide important clinical data. PN is the technique of artificial nutrition that provides the patient with fluids, energy and nutrients that are delivered directly to the circulatory system through the venous network. This non-physiological path of nutrient provision results in a dramatically different gastrointestinal response than that with enteral nutrition as PN pro-

vides no trophic effect on intestinal mucosa. Descriptions of protocols for determining constituents of PN for infants in hospitals and home settings are included.

Three chapters examine the role of the microbiome in the health of healthy as well as infants with serious GI-related diseases. As described by the authors, at birth, the intestine is sterile and colonic function of the human infant is immature. The development of the infant's microbiome is described in detail. The development of the colonic functions, including water absorption and carbohydrate fermentation, is related in part to the intestinal microbiota. These bacteria have well-established metabolic functions and perform important inmunoregulatory roles. Data from the human microbiome project has begun to identify and characterize the microorganisms found in both healthy and diseased individuals. The chapters objectively describe the functions of beneficial microorganisms that are consumed, and are referred to as probiotics, and nutritional sources for the probiotics, that are referred to as prebiotics. The microbiome contributes to the nutritional welfare of the infant through its metabolism of complex carbohydrates, generation of short-chain fatty-acids as an energy substrate for colonic epithelia, and production of folate and other B vitamins. Prebiotics have been found to selectively stimulate favorable growth and/or activity of selected probiotic bacteria in the colon. Probiotics have been shown to be beneficial in the treatment of acute infectious diarrhea as these reduce duration and stool frequency. We are reminded that optimal prebiotic usage as well as probiotic strains and dosages for preterm as well as full term infant patients still remain to be determined.

The final section of the second volume examines the newest research on the importance of long chain lipids in the growth of infants and also reviews the data linking early nutritional exposure to the risk of developing hypercholesterolemia, premature cardiovascular disease and obesity. The first chapter reviews in detail the value of lipid emulsions for the preterm and very preterm infant provided as either PN or enteral nutrition. The chapter includes a valuable discussion of the sources of oils used in available emulsions and provides recommendations based upon efficacy and safety data. Another chapter extensively reviews the roles of long chain omega-3 and omega-6 fatty acids in the neurological development and growth of the fetus and neonate with emphasis on the increased requirements in the preterm infant. The development of the brain and retina, visual and cognitive functions are reviewed and relevant epidemiological and intervention studies are tabulated. Recommendations for maternal intakes of long chain polyunsaturated fatty acids during pregnancy are included.

The balance between infant energy and growth requirements and increased risk of higher than normal serum lipids is compounded by genetic factors that predispose certain infants to premature cardiovascular disease. Relevant treatments, patient evaluation and review of the literature are provided in the next chapter. The mechanisms of action of adipose tissue cells, adipocytes, in regulating hunger, satiety and weight in utero as well as in infancy are examined in a separate chapter. Details concerning the effects of preterm birth followed by rapid weight gain and significantly increased risk of cardiovascular disease in adulthood are described. The receptors on adipocytes, hormones synthesized by adipocytes and their actions are reviewed.

The reader is reminded that currently there is no national or international agreed upon diagnostic cut off or definition of obesity in infants and young children. Strategies, from individual recommendations to public health measures are discussed and provide options for health providers. An overriding issue remains that there is no agreed-upon recommendation concerning when to begin screening for potential weight problems in infants, toddlers and young children. The two main hypotheses to explain the observed inverse association between small size at birth and adult disease are fetal programming i.e. the thrifty phenotype hypothesis and genetic susceptibility hypothesis. These, as well as future research areas and implications, are reviewed in detail in the following chapter. The book's final chapter examines the interactions between maternal behaviors and infant's weight gains. This unique chapter reviews the data that suggest that a mother can overfeed by virtue of failing to heed her infant's satiety signals, with a resultant heavier infant. The historic overview of studies on infant feeding practices in this chapter suggests that clinicians can help guide mothers to better read their infants' hunger and satiety cues to avoid overfeeding.

The logical sequence of the Sections as well as the chapters within each Section enhance the understanding of the latest information on the current standards of practice in infant feeding for clinicians, related health professionals including the dietician, nurse, pharmacist, physical therapist, behaviorist, psychologist and others involved in the team effort required for successful treatment of infants with relevant diseases and conditions that adversely affect normal metabolic processes. This comprehensive two volume resource also has great value for academicians involved in the education of graduate students and post-doctoral fellows, medical students and allied health professionals who plan to interact with parents of infants with disorders that may be beneficially affected by nutritional supports including enteral and parenteral nutritional modalities.

Cutting edge discussions of the roles of signaling molecules, growth factors, hormones, cellular and nuclear receptors and all of the cells and tissues directly involved or affected by the nutrients provided to infants, both term and preterm are included in well-organized chapters that put the molecular aspects into clinical perspective. Of great importance, the editors have provided chapters that balance the most technical information with discussions of its importance for clients and parents of patients as well as graduate and medical students, health professionals and academicians.

The volume contains over 200 detailed tables and figures that assist the reader in comprehending the complexities of breast milk, breastfeeding, other sources of infant nutrition as well as the biological significance of critical nutrients and the microbiome in maintaining infant growth and health. The over-riding goal of this volume is to provide the health professional with balanced documentation and awareness of the newest research and therapeutic approaches including an appreciation of the complexity of the interactions between genetics, intrauterine growth, maternal health, and term compared to preterm birth issues in this relatively new field of investigation. Hallmarks of the 60 chapters include key words and bulleted key points at the beginning of each chapter, complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. There are over 4000 up-to-date references; all chapters include a conclusion to highlight major findings. The volume also contains a highly annotated index.

This unique text provides practical, data-driven resources based upon the totality of the evidence to help the reader understand the basics, treatments and preventive strategies that are involved in the understanding the role dietary components may play in the early development of healthy infants as well as those with gastrointestinal diseases, genetic defects, metabolic or other complications and/or neurological impairments. Of equal importance, critical issues that involve parental concerns, such as food preferences in children, potential effects on weight gain or growth, breastfeeding versus formula feeding and differences in critical issues such as HIV infections in developing and developed nations are included in well-referenced, informative chapters. The overarching goal of the editors is to provide fully referenced information to health professionals so they may have a balanced perspective on the value of various preventive and treatment options that are available today as well as in the foreseeable future.

In conclusion, “Nutrition in Infancy”, edited by Professor Ronald Ross Watson, PhD, Professor George Grimble, PhD, Professor Victor R. Preedy, PhD, DSc, FRIPH, FRSH, FIBiol, FRCPath and Dr. Sherma Zibadi, MD, PhD provides health professionals in many areas of research and practice with the most up-to-date, well referenced and comprehensive volume on the current state of the science and medical practice guidelines with regard to maintaining the optimal nutritional status of the infant. This volume will serve the reader as the most authoritative resource in the field to date and is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, Ph.D., F.A.C.N., F.A.S.N.

Series Editor Bios

Dr. Adrianne Bendich has recently retired as Director of Medical Affairs at GlaxoSmithKline (GSK) Consumer Healthcare where she was responsible for leading the innovation and medical programs in support of many well-known brands including TUMS and Os-Cal. Dr. Bendich had primary responsibility for GSK's support for the Women's Health Initiative (WHI) intervention study. Prior to joining GSK, Dr. Bendich was at Roche Vitamins Inc. and was involved with the groundbreaking clinical studies showing that folic acid containing multivitamins significantly reduced major classes of birth defects. Dr. Bendich has coauthored over 100 major clinical research studies in the area of preventive nutrition. Dr. Bendich is recognized as a leading authority on antioxidants, nutrition and immunity and pregnancy outcomes, vitamin safety, and the cost-effectiveness of vitamin/mineral supplementation.

Dr. Bendich, who is now President of Consultants in Consumer Healthcare LLC, is the editor of ten books including "Preventive Nutrition: The Comprehensive Guide For Health Professionals," fourth edition coedited with Dr. Richard Deckelbaum, and is the Series Editor of "Nutrition and Health" for Springer/Humana Press (www.springer.com/series/7659). The Series contains 40 published volumes—major new editions in 2010–2011 include "Vitamin D," second edition edited by Dr. Michael Holick; "Dietary Components and Immune Function" edited by Dr. Ronald Ross Watson, Dr. Sherma Zibadi, and Dr. Victor R. Preedy; "Bioactive Compounds and Cancer" edited by Dr. John A. Milner and Dr. Donato F. Romagnolo; "Modern Dietary Fat Intakes in Disease Promotion" edited

by Dr. Fabien DeMeester, Dr. Sherma Zibadi, and Dr. Ronald Ross Watson; "Iron Deficiency and Overload" edited by Dr. Shlomo Yehuda and Dr. David Mostofsky; "Nutrition Guide for Physicians" edited by Dr. Edward Wilson, Dr. George A. Bray, Dr. Norman Temple, and Dr. Mary Struble; "Nutrition and Metabolism" edited by Dr. Christos Mantzoros, and "Fluid and Electrolytes in Pediatrics" edited by Leonard Feld and Dr. Frederick Kaskel. Recent volumes include "Handbook of Drug-Nutrient Interactions" edited by Dr. Joseph Boullata and Dr. Vincent Armenti; "Probiotics in Pediatric Medicine" edited by Dr. Sonia Michail and Dr. Philip Sherman; "Handbook of Nutrition and Pregnancy" edited by Dr. Carol Lammi-Keefe, Dr. Sarah Couch, and Dr. Elliot Philipson; "Nutrition and Rheumatic Disease" edited by Dr. Laura Coleman; "Nutrition and Kidney Disease" edited by Dr. Laura Byham-Grey, Dr. Jerrilynn Burrowes, and Dr. Glenn Chertow; "Nutrition and Health in Developing Countries" edited by Dr. Richard Semba and Dr. Martin Bloem; "Calcium in Human Health" edited by Dr. Robert Heaney and Dr. Connie Weaver, and "Nutrition and Bone Health" edited by Dr. Michael Holick and Dr. Bess Dawson-Hughes.

Dr. Bendich served as Associate Editor for "Nutrition" the International Journal; served on the Editorial Board of the *Journal of Women's Health and Gender-Based Medicine*, and was a member of the Board of Directors of the American College of Nutrition.

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Volume Editors Bios

Dr. George Grimble has been working in the area of Clinical Nutrition since 1980 with a special emphasis on clinical gastroenterology research, intensive care medicine and nutrition in older people. He is currently Principal Teaching Fellow at UCL in the Centre for Gastroenterology & Nutrition in the Division of Medicine.

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From 2007, he ran RECOMMEND (*Re*ading *Co*mmunity *Me*dical *N*utrition *D*ata) which investigated the attitudes of Family doctors towards nutrition and weight management. From 2008, he held concurrent appointments at Reading and UCL, running M.Sc. programs in both universities.

Dr. Grimble is a very active teacher in graduate programs and has published extensively. He is currently preparing his seventh book, has more than 250 scientific publications which include 74 reviews and book chapters and two patents. He has acted as consultant for many companies active in clinical nutrition support.

Professor **Victor R. Preedy B.Sc. D.Sc. FSB FRCPath FRSPH** is currently Professor of Nutritional Biochemistry in the Department of Nutrition and Dietetics, King's College London and Honorary Professor of Clinical Biochemistry in the Department of Clinical Biochemistry, King's College Hospital. He is also Director of the Genomics Centre, Kings College London and a member of the School of Medicine, King's College London. King's College London is one of the world's leading

universities. Professor Preedy gained his Ph.D. in 1981 and in 1992 he received his Membership of the Royal College of Pathologists (MRCPath), based on his published works. He was elected a Fellow of the Royal College of Pathologists (FRCPath) in 2000. In 1993 he gained his second doctorial degree (DSc) for his outstanding contribution to protein metabolism. In 2004 Professor Preedy was elected as a Fellow to both the Royal Society for the Promotion of Health (FRSH) and The Royal Institute of Public Health (FRIPHH). In 2009 he was elected as a Fellow of the Royal Society for Public Health (RSPH). He is also a Fellow of The Society of Biology (FSB). Professor Preedy has written or edited over 550 articles, which includes over 160 peer-reviewed manuscripts based on original research and 85 reviews and 30 books. His interests pertain to matters concerning nutrition and health at the individual and societal levels.

Ronald R. Watson, Ph.D., attended the University of Idaho but graduated from Brigham Young University in Provo, Utah, with a degree in chemistry in 1966. He earned his Ph.D. in biochemistry from Michigan State University in 1971. His postdoctoral schooling in nutrition and microbiology was completed at the Harvard School of Public Health, where he gained 2 years of postdoctoral research experience in immunology and nutrition.

From 1973 to 1974 Dr. Watson was assistant professor of immunology and performed research at the University of Mississippi Medical Center in Jackson. He was assistant professor of microbiology and immunology at the Indiana University Medical School from 1974 to 1978 and associate professor at Purdue University in the Department of Food and Nutrition from 1978 to 1982. In 1982 Dr. Watson joined the faculty at the University of Arizona Health Sciences Center in the Department of Family and Community Medicine of the School of Medicine. He is currently professor of health promotion sciences in the Mel and Enid Zuckerman Arizona College of Public Health.

Dr. Watson is a member of several national and international nutrition, immunology, cancer, and alcoholism research societies. Among his patents he has one on a dietary supplement; passion fruit peel extract with more pending. He had done DHEA research on its effects on mouse AIDS and immune function for 20 years. He edited a previous book on melatonin (Watson RR. *Health Promotion and Aging: The Role of Dehydroepiandrosterone* (DHEA). Harwood Academic Publishers, 1999, 164 pages). For 30 years he was funded by Wallace Research Foundation to study dietary supplements in health promotion. Dr. Watson has edited more than 100 books on nutrition, dietary supplements and over-the-counter agents, and drugs of abuse as scientific reference books. He has published more than 500 research and review articles.

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Part I
Nutrition and Neonatal/Infant Disease

Chapter 1
Growth and Body Composition in Children with Chronic Disease

Kelly A. Dougherty and Virginia A. Stallings

Key Points

- Studies of children with cerebral palsy indicate growth is compromised throughout life and the more severe the motor deficit, the greater the degree of growth failure
- In general, children with cerebral palsy have reduced body fat and fat-free mass, though the differences are small for children with milder forms of cerebral palsy
- Postnatal growth retardation is a clearly identified feature of Down syndrome
- Down syndrome is characterized by a wide range of phenotypic abnormalities including altered head and facial growth, disproportionately short proximal limb growth, and organ abnormalities
- Overweight/obesity is common in children with Down syndrome beginning in late infancy and early childhood

Keywords Growth • Body composition • Chronic disease • Nutrition • Cerebral palsy • Down syndrome

Introduction

Adequate nutrition is essential for normal growth and development. Children with chronic disease may have functional limitations due to a physically based disorder of prenatal (genetic, disruption of fetal development), perinatal (late pregnancy or delivery), or postnatal origin likely with accompanying alterations in dietary intake, metabolism, growth, and activity resulting in body composition that differs from the healthy child. This chapter, which is an update of previous work [1], describes two contrasting models of altered body composition in children; those with cerebral palsy (CP) and Down syndrome (DS), both prevalent disorders with a differing etiology and impact on growth, body composition, and nutritional status. These differences require separate approaches for accurate nutrition-related clinical assessment and management.

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Cerebral Palsy

Background

Cerebral palsy is defined as "a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributable to nonprogressive disturbances that occurred in the developing fetal or infant brain [2]." CP affects 2.5 in 1,000 births in the United States [3] with the most common etiology being anoxia around the time of birth, often due to difficulties at delivery. Disability in CP varies widely depending upon the extent and motor systems affected. About 80% of children with CP have some type of movement disorder [3], with the most common classifications being *spastic* (stiff and difficult movement), *dyskinetic* (involuntary and uncontrolled movement), and *ataxic* (disturbed sense of balance and depth perception). Limbs affected by the disorder may include one *(monoparesis)*, two *(hemiparesis, diplegia)*, three *(triplegia)*, or all four *(quadriplegia)*. In children with CP, the valid and reliable classification system for impairments in gross motor function most commonly used in clinical and research settings is the Gross Motor Function Classification System-Expanded and Revised (GMFCS-ER) [4], which rates severity of symptoms ranging from 1 (low) to 5 (high).

Growth Characteristics

Since increases in body size are highly correlated with increases in fat-free mass (FFM), body weight serves as a rough indicator of changes in FFM when direct body composition measures are unavailable. By measuring height or a limb length, studies of children with CP indicate growth is compromised throughout life and the more severe the motor deficit, the greater the degree of growth failure. Early investigations assumed that growth failure was due to the underlying brain disorder, some set of factors linked to it (e.g., central nervous system (CNS) damage, lack of normal activity, altered energy expenditure, limb atrophy, scoliosis), or chronic malnutrition [5]. More recent studies have strongly implicated malnutrition as a frequent cause of growth failure, particularly among severely affected children [6–11]. Because of the cognitive and physical heterogeneity found in children with CP, growth delays vary greatly.

Studies which have used traditional anthropometic tools to assess stature suggest that overall, children with quadriplegic CP are about 1.5 standard deviations (SD) below average (between fifth and tenth centiles) for body size; those with hemi or diplegia are reduced by less than 0.5 SD (between twenty-fifth and fiftieth centiles). Since accurate stature is difficult or impossible to measure in this population of children, alternative measures (upper arm or lower leg lengths) are used to assess growth [12–14]. Among children with quadriplegic CP, size is usually less than the third centile with significantly greater deficits in lower leg than upper arm length. Hemiplegic and diplegic children have proportionate reductions in each dimension of around 0.5 SD (near the twenty-fifth centile).

Cross-sectional studies [7, 12, 15] show that children with severe CP display progressively greater growth failure with age probably due to the cumulative effects of various factors including nutritional, CNS, contractures, and scoliosis. Age-specific measures of growth are closer to normal in infancy and toddlerhood (around tenth centile), but substantially less than the third centile by mid-childhood. During adolescence, the degree of growth failure is increased by a reduction in the pubertal growth spurt. By the oldest pre-adult ages, body size is sometimes reduced by as much as 3 SD below the average. Among children with milder CP, those <6 years of age may have slightly greater linear growth deficiency than older children [6]. Improvements with age appear to be associated with better nutritional status and higher levels of body fat, possibly due to improved oral motor functioning as feeding and other developmental milestones are achieved.

As indicated above, children with more severe disease including seizure disorders where all four limbs are involved and those with the greatest degree of hypertonicity demonstrate both the most substantial growth failure and the greatest compromise in body fat and FFM. However, feeding difficulties associated with poor oral motor functioning almost inevitably affect these children and contribute to under-nutrition [16–19]. Thus nutritional compromise and disease severity confound each other. A substantial number of studies have demonstrated an association between poor growth and feeding abnormalities. Stallings et al. [7] separated the effects of disease severity and other factors (i.e., age, gender, and ethnicity) contributing to growth failure in children 2–18 years of age with quadriplegic CP using a two step regression procedure. For children <8 years, the impact of nutritional status (assessed by body fat measures) on growth was larger than in children >8 years. This age difference probably reflects the irremediable effects of long-term under-nutrition on growth of older children who ultimately reach skeletal maturation (i.e., loss of linear growth potential) in spite of chronic malnutrition. Nutritional status may also contribute to the milder growth deficiency in children with hemiplegia and diplegia with significant correlations between size, fat, and muscle measurements in these children [6].

Established in 1996, the North American Growth in Cerebral Palsy Project (NAGCPP) research program investigated growth, nutrition, functional outcomes, and overall quality of life in children with CP. The goal was to define growth patterns, determine the nutrition, endocrine, neurologic, and physical factors influencing growth and to investigate how growth affects function, general health status, cognitive and motor development, family stress, health care use, morbidity, and mortality [20]. Subjects were recruited from six centers in the United States and Canada. Results from NAGCPP showed that in children ages 2–18 years with moderate to severe CP (GMFCS III to V) parent reported feeding dysfunction was strongly associated with poor health and nutritional status as well as severity of motor impairment. Those orally fed (non-tube fed) displayed a dose response relationship between severity of feeding dysfunction and growth and body fat (energy) stores, suggesting a pattern of inadequate energy intake. The authors recommended using a structured feeding dysfunction questionnaire to screen for nutritional risk in children with CP [21]. Similar findings from a large population-based cohort study conducted in England showed that feeding difficulties reported by parents in the first 4 weeks of life in children with CP were associated with more severe neurodevelopmental impairments and an increased likelihood of being underweight by school age, suggesting that early, persistent and severe feeding difficulties are a marker for future growth failure [19].

Body Composition and Nutritional Status

In general, children with CP have reduced body fat and FFM, though the differences are small for children with milder forms of CP. Children with severe CP have been found to be deficient in both fat mass (FM) and FFM by various measures [6–8, 12, 22–24]. Anthropometric measures of body fat (e.g., triceps and other skinfold sites, percent body fat computed from skinfolds) indicate that body fat stores are reduced by 0.5–1.0 SD (between tenth and twenty-fifth centiles) for children with quadriplegic CP and by about 0.3 SD (between twenty-fifth and fiftieth centiles) for children with less severe CP [6, 7]. Arm muscle area (an indicator of muscle mass [25]) is around tenth centile for quadriplegic CP children, but near the median on average for children with hemiplegic and diplegic CP. A study from the NAGCPP confirmed these earlier findings showing that a population based sample of children with moderate to severe CP were malnourished, displayed low fat stores, decreased muscle mass and short stature [24]. Hospitalizations, physician visits, missed school days, days spent in bed, and inability to perform usual activities were greater in children with CP with lower energy stores, suggesting poorer health status and limitations in societal participation.

Estimates of Body Composition in Severe CP

Stallings et al. [8] evaluated relative FFM and FM in pre-pubertal children with quadriplegic CP compared with a group of healthy control children. FM in these children was reduced to about 60% of the control value (2.9 vs. 4.6 kg in control), and FFM by about 75% (13.5 vs. 17.6 kg) using deuterium oxide dilution. (D_2O). Anthropometric estimates of FM and FFM [26] yielded even lower estimates (47% for FM, 69% for FFM). Regression analyses indicated that black children were at risk for even lower fat stores (on average, 1.8 kg less than white children) and those with gastrostomy tubes had higher fat stores (on average 1.7 kg greater than those without tubes). The reduced fat stores in black children may be an artifact of the expected greater bone density and lower body fat levels seen in otherwise healthy black children [25, 27].

Centripetal Fat Pattern

Similar to other conditions associated with chronic nutritional deprivation, children with severe CP have a centripetal fat pattern where the fat on the arm (triceps site) is differentially more depleted than that on the body (subscapular site). This was first documented by Spender et al. [28] and later replicated by Stallings et al. [8]. Thus, exclusive use of the triceps skinfold as an indicator of subcutaneous fat stores may underestimate total body FM in these children. Simple correlations showed that the best estimate of percent body fat in children with CP (using D_2O as the standard) is the Slaughter et al. equation [26] which uses triceps and subscapular skinfold measurements [8].

Clinical Assessment in Children with Cerebral Palsy

Growth assessment for children with CP should follow many of the procedures used in a standard of care pediatric examination, including accurate and reproducible measurements of stature (recumbent length or height) and weight, head circumference in younger children and measurement of one (triceps) or more (biceps, subscapular or suprailiac) skinfolds to determine body fat stores. These measures should be made accurately [29] using standard equipment and techniques. Results are plotted on a growth chart [30] or compared to other reference data that are based on a large sample that reflects the growth of healthy children. As discussed previously, the growth pattern for children with CP may be drastically different from those of their healthy counterparts. Krick et al. [15] provided the first CP specific growth charts for height, weight and weight for height for children with quadriplegic CP. These charts were developed using tools of unknown reliability and malnourished children were not excluded from the sample.

Since stature measurement accuracy is usually poor in children with severe CP, special approaches to linear growth assessment should also be instituted [31]. Spender et al. [12] first suggested using upper arm and/or lower leg length as alternatives to height measures for difficult to measure children. These measures have a high correlation with stature in healthy children (around 0.8), and are particularly useful for children >3–4 years of age. Stevenson [14] evaluated a convenient sample of younger children with CP using these same measures and knee height, using only children with CP whose height/recumbent length could be measured. The correlation between height and each of the three measurements was around 0.97, indicating that such measures are a strong proxy for height.

Stallings and Zemel [13] developed reference charts for upper arm and lower leg length drawn from a sample of healthy children 3–18 years old on which such measurements of children with CP are plotted. Using these charts, the clinician compares linear growth of a child with CP to that of healthy, same age, and gender children. It is an approach yielding a proxy for height age to be used to

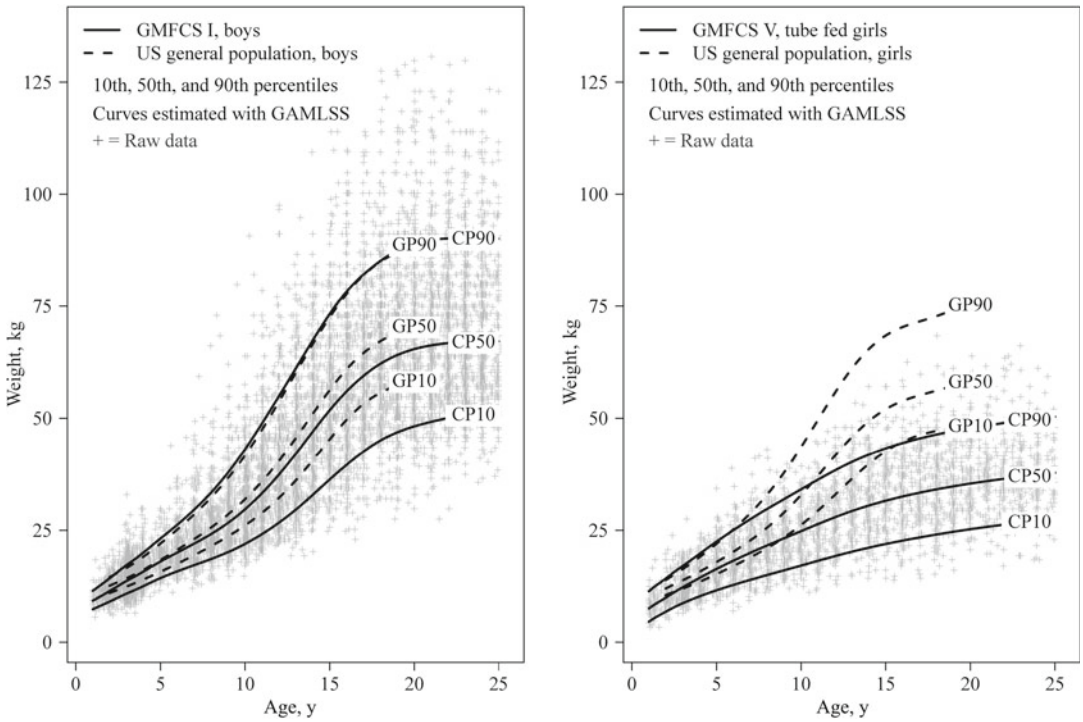

Fig. 1.1 Scatter plots of weight for age for boys with cerebral palsy (CP) in Gross Motor Function Classification System (GMFCS) level I (*left*) and tube fed girls with CP in GMFCS level V (*right*). Also plotted are estimated weight for age percentiles for GMFCS I boys with CP (*left*) and GMFCS V tube fed girls with CP (*right*) compared to respective Center for Disease Control percentiles in the general population (GP). Reproduced with permission from Pediatrics, Vol. 128, Page(s) e299–e307, Copyright © 2011 by the AAP

assess the child's weight for height. In contrast, Stevenson recommended use of either lower leg length (measurable with a steel tape) or knee height (measurable with a modestly priced caliper) and computation of height using the following equations:

Upper arm length:	stature (cm) = 21.8 + (4.35 × upper arm length)
Lower leg (tibial) length:	stature (cm) = 30.8 + (3.26 × lower leg length)
Knee height:	stature (cm) = 24.2 + (2.69 × knee height)

The computed stature values are plotted on a growth chart for healthy children [30]. This approach allows a weight for height determination to be made. The equations, however, are only valid for children 12 years and under. Equations developed to estimate height from knee height in a healthy population [32] are recommended to be used for estimating height in adolescents and adults with CP. The NAGCPP produced growth curves for weight, knee height, upper arm length, mid-upper arm muscle area, triceps skinfold and subscapular skinfold for children with moderate to severe CP [33]. Height, weight, and BMI growth charts stratified by motor and feeding skills in children with CP [34] showed that those with minimal motor dysfunction achieved weights and heights similar to sex and age matched healthy children. However, those with significant motor dysfunction and/or feeding difficulties displayed significantly attenuated weight and heights compared to those achieved by healthy children, suggesting standard growth charts should not be used to monitor growth of children with CP. Tibia length growth curves for ambulatory children with CP (GMFCS levels I, II, and III) also exist [35]. Recently, Brooks et al. [36] published growth charts for weight stratified by age and GMFCS which were constructed from over 100,000 weight measures in children with CP (Fig. 1.1). These charts

were designed to mimic the Center for Disease Control charts and there were no inclusion criteria for good to optimal nutritional status. Studies are needed to establish their utility in clinical care and effectiveness in recognizing unhealthy weights to support treatment changes.

Nutritional status assessment identifies children who are over or undernourished. Approaches to dietary intake were reviewed by Stallings and Zemel [8]. Body fat may be assessed in children with CP by measurement of triceps and subscapular skinfold thickness [29]. Percent body fat can be calculated using the equations from Slaughter et al. [26] as follows:

All females: % body fat = 1.33 (triceps + subscapular)–0.013 (triceps + subscapular)^2–2.5
Prepubescent white males: % body fat = 1.21 (triceps + subscapular)–0.008 (triceps + subscapular)^2–1.7
Prepubescent black males: % body fat = 1.21 (triceps + subscapular)–0.008 (triceps + subscapular)^2–3.2

In overweight subjects, when the sum of triceps and subscapular skinfolds is >35 mm, the following equations are used:

All females: % body fat = 0.546 (triceps + subscapular) + 9.7
All males: % body fat = 0.783 (triceps + subscapular) + 1.6

Values for summed triceps and subscapular skinfolds (in mm) can also be used and compared to reference data from the National Health and Nutrition Examination surveys I and II provided in Frisancho [25]. Estimation of percent body fat using skinfold measures should be made with caution in severely affected children with CP because of the disproportionality of total body fat compared to healthy, physically active children from which the estimation equations were developed [37].

Down Syndrome

Background

Down syndrome (DS) is a relatively common genetic disorder caused by the presence of an extra chromosome number 21 that usually results from a non-disjunction during meiotic cell division in the gametes. Approximately 5,500 children with DS are born in the United States each year, or about 1 in every 650–1,000 live births [38]. DS is characterized by a wide range of phenotypic abnormalities including altered head and facial growth, disproportionately short proximal limb growth and organ abnormalities (including heart defects in up to 40% of affected children). Children are often hypotonic and hyper-reflexic as infants, though these abnormalities are ameliorated, to some extent, with age. Cognitive delays occur commonly and are usually moderate. However, in the United States with the growth of early intervention, individual educational programming and mainstreaming, many children achieve more developmental accomplishments.

Growth Characteristics

Postnatal growth retardation is a clearly identified feature of DS [39–42]. Compared to healthy children, birth length and weight are slightly reduced (≤1 cm in both genders) and a progressive reduction in average length is apparent with mean values 2 cm less than normal at 3 months and 3.5 cm less than normal by 3 years. There is, however, great variability in growth with some children well within the range of normal variation, whereas others are reduced by several SD. These size reductions are manifest in reduced growth velocities (rates), with the average child with DS growing 38 cm in 3 years

compared with 46 cm of growth typical for healthy children. Similar reduction in weight and weight velocity are apparent during early infancy, reflecting reduced FFM accretion during this period. Velocity of weight gain is reduced by as much as 22% less than healthy children; however between 18 and 36 months, weight velocity is comparable.

From early childhood until about 11 or 12 years of age for girls and 15 or 16 years of age for boys, the difference in height between children with DS and healthy children is similar, reflecting relatively more normal changes in growth and FFM. However, there is continued slow growth velocity in height (between third and twenty-fifth centiles). Weight velocities for this same period show a more typical pattern (between twenty-fifth and fiftieth centiles), again indicating overweight/obesity relative to height. After these ages, the distance between growth curves for children with DS and healthy children increases.

During adolescence, height is reduced by 2–4 SD below the normal mean and by the end of adolescence, by 3.5–4 SD. Peak pubertal growth spurt ranges from about 5–13 cm/year (similar or low compared to healthy adolescents), and these spurts occur at ages similar to those of healthy children. Final height may be reached earlier than in healthy children (15 years in boys, 14.3 years in girls). Boys with DS may have an even more attenuated pubertal growth spurts compared to girls with DS.

Direct Measurements of Body Composition

As indicated above, overweight/obesity is common in children with DS beginning in late infancy and early childhood with prevalence rates ranging from 30 to 36% [41–43]. Analyses of weight for height and body mass index [39, 44] indicates that between 2 and 12 years of age measures of body fatness for children with DS are above normal. Values of weight for height are clearly above those for healthy children beginning at about the 100 cm interval for height (around 4–6 years of age) and remain above the normal mean for all remaining age intervals.

Median values for body mass index (weight/height^2) are less than those for healthy children from about 3 months to 2 years of age. Thereafter, they are greater than normal, usually between seventy-fifth and ninety-fifth centiles throughout childhood and adolescence. Pseudo-velocities (i.e., growth velocities estimated from the difference of average weights at successive ages) for weight are between twenty-fifth and seventy-fifth centiles for healthy children throughout childhood but increase to ninetieth centile during adolescence. Because height velocities during this age interval are often below healthy children for adolescents with DS, the percentage of these children who are overweight/obesity or the degree of overweight/obesity probably increases during adolescence.

Body Composition

Few studies directly measuring body composition have been conducted on children with DS. A small sample of prepubescent children aged 5–11 years were assessed for body composition, dietary intake, and energy expenditure and compared to a control group of healthy children [45]. Unfortunately, since the control group was selected so that their percentage of ideal body weight would be similar to that of the DS group, this confounded comparison of body composition between the two groups. Despite excellent similarities between the two groups in BMI, percentage body fat, % ideal body weight, and FFM, resting energy expenditure was reduced in the children with DS compared to the control group. This reduction in resting energy expenditure adjusted for body size and composition may contribute to the increase risk for obesity in children and adults with DS.

Clinical Assessment in Children with DS

As with children with CP, growth and body composition assessment for children with DS should follow the procedures used in a standard of care pediatric examination. Accurate measurements of recumbent length or standing height and weight, head circumference in younger children, and measurement of one (triceps) or more (biceps, subscapular, and suprailiac) skinfold sites where possible to determine body fat stores more directly should be taken. These measures should be made accurately [29] using standard equipment and plotted on a growth chart [30]. In addition, height/recumbent length and weight should be plotted on growth charts specifically for children with DS [43]. Reference data for weight for height [44] or body mass index can also be used to evaluate relative body fatness. However these growth charts for US children with DS are not optimal and are outdated. Currently, a study is underway to prospectively collect growth measures in a contemporary, multiethnic sample of US infants, children, and adolescents with DS to develop growth charts for head circumference, length/height, weight, and body mass index.

References

1. Cronk C, Fung E, Stallings VA. Body composition in children with special health care needs. In: Grimble GK, Preedy VR, Watson RR, editors. Nutrition in the infant: problems and practical procedures. London: Greenwich Medical Media, Ltd.; 2001. p. 31–8.
2. Rethlefsen SA, Ryan DD, Kay RM. Classification systems in cerebral palsy. Orthop Clin North Am. 2010;41:457–67.
3. Delgado MR, Albright AL. Movement disorders in children: definitions, classifications, and grading systems. J Child Neurol. 2003;18 Suppl 1:S1–8.
4. Palisano RJ, Rosenbaum P, Bartlett D, Livingston MH. Content validity of the expanded and revised gross motor function classification system. Dev Med Child Neurol. 2008;50:744–50.
5. Cronk C, Stallings VA. Growth in children with cerebral palsy. Mental Retard Develop Disab Res Rev. 1997;3:129–37.
6. Stallings VA, Charney EB, Davies JC, Cronk CE. Nutritional status and growth of children with diplegic or hemiplegic cerebral palsy. Dev Med Child Neurol. 1993;35:997–1006.
7. Stallings VA, Charney EB, Davies JC, Cronk CE. Nutrition-related growth failure of children with quadriplegic cerebral palsy. Dev Med Child Neurol. 1993;35:126–38.
8. Stallings VA, Cronk CE, Zemel BS, Charney EB. Body composition in children with spastic quadriplegic cerebral palsy. J Pediatr. 1995;126:833–9.
9. Stallings VA, Zemel BS, Davies JC, Cronk CE, Charney EB. Energy expenditure of children and adolescents with severe disabilities: a cerebral palsy model. Am J Clin Nutr. 1996;64:627–34.
10. Samson-Fang LJ, Stevenson RD. Identification of malnutrition in children with cerebral palsy: poor performance of weight-for-height centiles. Dev Med Child Neurol. 2000;42:162–8.
11. Schoendorfer N, Boyd R, Davies PS. Micronutrient adequacy and morbidity: paucity of information in children with cerebral palsy. Nutr Rev. 2010;68:739–48.
12. Spender QW, Cronk CE, Charney EB, Stallings VA. Assessment of linear growth of children with cerebral palsy: use of alternative measures to height or length. Dev Med Child Neurol. 1989;31:206–14.
13. Stallings VA, Zemel BS. Nutritional assessment of the disabled child. In: Sullivan PB, Rosenbloom L, editors. Feeding the disabled child (Clinics in Developmental Medicine). 140th ed. London: Mac Keith Press; 1996. p. 62–76.
14. Stevenson RD. Use of segmental measures to estimate stature in children with cerebral palsy. Arch Pediatr Adolesc Med. 1995;149:658–62.
15. Krick J, Murphy-Miller P, Zeger S, Wright E. Pattern of growth in children with cerebral palsy. J Am Diet Assoc. 1996;96:680–5.
16. Thommessen M, Heiberg A, Kase BF, Larsen S, Riis G. Feeding problems, height and weight in different groups of disabled children. Acta Paediatr Scand. 1991;80:527–33.
17. Krick J, Van Duyn MA. The relationship between oral-motor involvement and growth: a pilot study in a pediatric population with cerebral palsy. J Am Diet Assoc. 1984;84:555–9.

18. Dahl M, Gebre-Medhin M. Feeding and nutritional problems in children with cerebral palsy and myelomeningocoele. Acta Paediatr. 1993;82:816–20.
19. Motion S, Northstone K, Emond A, Stucke S, Golding J. Early feeding problems in children with cerebral palsy: weight and neurodevelopmental outcomes. Dev Med Child Neurol. 2002;44:40–3.
20. Liptak GS, O'Donnell M, Conaway M, et al. Health status of children with moderate to severe cerebral palsy. Dev Med Child Neurol. 2001;43:364–70.
21. Fung EB, Samson-Fang L, Stallings VA, et al. Feeding dysfunction is associated with poor growth and health status in children with cerebral palsy. J Am Diet Assoc. 2002;102:361–73.
22. Dahlseng MO, Finbraten AK, Juliusson PB, Skranes J, Andersen G, Vik T. Feeding problems, growth and nutritional status in children with cerebral palsy. Acta Paediatr. 2011;101:92–8.
23. Azcue MP, Zello GA, Levy LD, Pencharz PB. Energy expenditure and body composition in children with spastic quadriplegic cerebral palsy. J Pediatr. 1996;129:870–6.
24. Samson-Fang L, Fung E, Stallings VA, et al. Relationship of nutritional status to health and societal participation in children with cerebral palsy. J Pediatr. 2002;141:637–43.
25. Frisancho AR. Anthropometric standards for assessment of growth and nutritional status. Ann Arbor: University of Michigan Press; 1990.
26. Slaughter MH, Lohman TG, Boileau RA, et al. Skinfold equations for estimation of body fatness in children and youth. Hum Biol. 1988;60:709–23.
27. Bell NH, Shary J, Stevens J, Garza M, Gordon L, Edwards J. Demonstration that bone mass is greater in black than in white children. J Bone Miner Res. 1991;6:719–23.
28. Spender QW, Cronk CE, Stallings VA, Hediger ML. Fat distribution in children with cerebral palsy. Ann Hum Biol. 1988;15:191–6.
29. Lohman TG, Roche AR, Martorell R. Anthropometric standardization reference manual. Champaign: Human Kinetics; 1988.
30. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. Advance data from vital and health statistics. 314th ed. Hyattsville, MD: National Center for Health Statistics; 2000. p. 1–28.
31. Stevenson RD. Measurement of growth in children with developmental disabilities. Dev Med Child Neurol. 1996;38:855–60.
32. Chumlea WC, Guo SS, Steinbaugh ML. Prediction of stature from knee height for black and white adults and children with application to mobility-impaired or handicapped persons. J Am Diet Assoc. 1994;94:1385–8. 1391.
33. Stevenson RD, Conaway M, Chumlea WC, et al. Growth and health in children with moderate-to-severe cerebral palsy. Pediatrics. 2006;118:1010–8.
34. Day SM, Strauss DJ, Vachon PJ, Rosenbloom L, Shavelle RM, Wu YW. Growth patterns in a population of children and adolescents with cerebral palsy. Dev Med Child Neurol. 2007;49:167–71.
35. Oeffinger D, Conaway M, Stevenson R, Hall J, Shapiro R, Tylkowski C. Tibial length growth curves for ambulatory children and adolescents with cerebral palsy. Dev Med Child Neurol. 2010;52:e195–201.
36. Brooks J, Day S, Shavelle R, Strauss D. Low weight, morbidity, and mortality in children with cerebral palsy: new clinical growth charts. Pediatrics. 2011;128:e299–307.
37. van den Berg-Emons RJ, van Baak MA, Westerterp KR. Are skinfold measurements suitable to compare body fat between children with spastic cerebral palsy and healthy controls? Dev Med Child Neurol. 1998;40:335–9.
38. Bittles AH, Bower C, Hussain R, Glasson EJ. The four ages of Down syndrome. Eur J Public Health. 2007;17:221–5.
39. Cronk CE. Growth retardation in children with Down syndrome. In: S.Castells, H.Wisniewski, eds. *Growth hormone treatment in Down syndrome: Proceedings of an International Conference*. New York: John Wiley and Sons; 1993;13–32.
40. Kimura J, Tachibana K, Imaizumi K, Kurosawa K, Kuroki Y. Longitudinal growth and height velocity of Japanese children with Down's syndrome. Acta Paediatr. 2003;92:1039–42.
41. Myrelid A, Gustafsson J, Ollars B, Anneren G. Growth charts for Down's syndrome from birth to 18 years of age. Arch Dis Child. 2002;87:97–103.
42. Styles ME, Cole TJ, Dennis J, Preece MA. New cross sectional stature, weight, and head circumference references for Down's syndrome in the UK and Republic of Ireland. Arch Dis Child. 2002;87:104–8.
43. Cronk C, Crocker AC, Pueschel SM, et al. Growth charts for children with Down syndrome: 1 month to 18 years of age. Pediatrics. 1988;81:102–10.
44. Cronk CE, Chumlea WC, Roche AF. Assessment of overweight children with trisomy 21. Am J Ment Defic. 1985;89:433–6.
45. Luke A, Roizen NJ, Sutton M, Schoeller DA. Energy expenditure in children with Down syndrome: correcting metabolic rate for movement. J Pediatr. 1994;125:829–38.

Chapter 2
Nutritional Support in Inborn Errors of Metabolism

Juan J. Diaz, Marilyn Bernard, Lauren Furuta, and Clifford Lo

Key Points

- The treatment of many inborn errors of metabolism is often nutritional, involving alterations in protein, carbohydrate, fat, or energy intake.
- Dietary manipulations should be undertaken with a physician who is familiar with the disorders and an experienced dietician.
- The goal should be not only to prevent adverse outcomes but also to assist families and patients to incorporate their special diets into a lifestyle that is as normal and as healthy as possible.

Keywords Inborn errors of metabolism • Protein metabolism • Fat metabolism • Carbohydrate metabolism

Introduction

Inborn errors of metabolism are disorders caused by genetic defects that produce problems in normal metabolic processes. [1] Although each single gene disease is relatively rare, many more diseases have had their genetic basis elucidated because of recent research into the human genome. In a normal metabolic pathway, a substrate is converted into a product in a chemical reaction catalyzed by an enzyme, sometimes helped by a coenzyme. A genetic mutation producing a defective enzyme or cofactor is usually responsible for these diseases. Signs and symptoms of these disorders may appear

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due to the accumulation in blood or in other tissues of the substrate, to the production of toxic metabolites because of the use of alternative metabolic pathways, or to the lack of the final product. They result from variations in the structure and function of enzymes or other proteins. The aim of treatment is to correct the biochemical abnormality and may include the following:

1. Restriction of the accumulated substrate.
2. Enhancement of mutant enzyme by supplying larger doses of coenzyme.
3. Provision of alternate pathways for the accumulated substrate.

Historical Background

The first inborn error of metabolism to be successfully managed nutritionally was phenylketonuria (PKU). In 1953, Bickel et al. documented that restriction of phenylalanine lowered blood concentrations of phenylalanine and prevented the severe manifestations associated with untreated PKU [2]. Since then, the development of diet therapies for other inborn errors has occurred relatively swiftly.

A high index of suspicion is needed for the diagnosis of these disorders as their clinical symptoms are usually nonspecific. Fortunately, the development of tandem mass spectrometry in the late 1990s allowed the neonatal detection of multiple disorders in a single blood spot, so that treatment could be initiated before those symptoms occur.

Nutritional evaluation involves assessment of growth, nutrient intake, and biochemical parameters. Treatment of most metabolic disorders requires the restriction of at least one nutrient or dietary component. However, adequate energy intake is essential for both normal growth and the prevention of unnecessary catabolism. Most disorders require the use of a specialized semisynthetic formula (or medical food) to meet the nutritional requirements. For disorders of protein metabolism, specialized nitrogen-free foods (pastas, breads, baked products) are typically needed to provide adequate calories.

Disorders of Amino Acid Metabolism

Hyperphenylalaninemias

PKU (OMIM 261600) is caused by a defect in the enzyme phenylalanine hydroxylase (PAH), which results in the inability to convert the amino acid phenylalanine (Phe) to tyrosine. Phenylalanine and its metabolites accumulate in the blood and other body tissues [3].

Untreated, PKU eventually progresses to damage to the brain and central nervous system, most likely due to competition between elevated phenylalanine and other amino acids for transport into the brain, hypomyelination, and impaired development of central nervous system white matter [4].

PAH deficiency can be classified into the following categories [5]:

Classic PKU: A complete or near-complete deficiency of PAH activity is observed. This patients tolerate less than 250–350 mg of dietary Phe per day to keep plasma concentration at a safe level of no more than 300 μmol/L (5 mg/dL). Blood tyrosine levels may be normal or low

Moderate PKU: Patients with a tolerance 350–400 mg of dietary Phe per day.

Mild PKU: Tolerance of 400–600 mg of Phe per day.

Mild hyperphenylalaninemia. These patients show plasma Phe concentrations lower than 600 μmol/L (10 mg/dL) on a normal diet.

Some authors call this group benign hyperphenylalaninemia because there is no need to treat this disorder. Phe levels may be a concern for women as they reach their child-bearing years.

Rare defects in tetrahydrobiopterin (BH4), the cofactor for PAH, can also cause elevated phenylalanine levels. Metabolism of tyrosine and tryptophan is dependent on this cofactor, so a defect in BH4 also leads to neurological problems from neurotransmitter deficiencies. Treatment involves early diagnosis by urine studies, supplementation with a combination of neurotransmitter precursors, BH4 and folinic acid [6], and in some cases a reduced phenylalanine diet.

Dietary Management of Hyperphenylalaninemias

Restriction of phenylalanine beginning in infancy results in the lowering of phenylalanine levels and the prevention of mental retardation. The dietary treatment allows for a prescribed amount of phenylalanine, which is an essential amino acid, to allow appropriate growth and development while maintaining phenylalanine levels at 2–6 mg/dL [7]. Tolerance for dietary phenylalanine varies with the severity of the enzyme defect, Special medical formulas that contain all the amino acids except phenylalanine are required for assuring an adequate protein intake. The medical formulas are supplemented with vitamins and minerals.

The diet of an infant with PKU consists of a prescribed amount of regular formula or breastmilk combined with a PKU formula. The appropriate phenylalanine requirement is determined by the initial phenylalanine level and subsequent levels once diet is initiated. Breastfeeding is encouraged, but must be managed closely to avoid excess phenylalanine ingestion. The practical method of management consists of alternating between breastfeedings and special formula feedings. Phenylalanine levels are measured once per week, and the diet is adjusted accordingly to keep blood levels in the appropriate range.

As the child ages, solid foods are introduced. The allowed foods include only those that are naturally low in protein such as vegetables, fruits, and some grain products. Special food products that have been modified to be low in protein are an important source of calories, bulk, and variety. Resources are available to help estimate the phenylalanine content of foods [8].

The diet for PKU was originally discontinued during early childhood around age 5 years. It has now been determined that this practice was detrimental to some children's development. The current recommendation is to continue phenylalanine restriction throughout life [9, 10]. Compliance with the low-Phe diet is often poor owing to restriction in natural foods and the requirement for consumption of a phenylalanine-free formula.

Glycomacropeptide (GMP), a natural whey protein produced during cheese production, is uniquely suited to a low-Phe diet because it contains minimal Phe (2.5–5 mg Phe/g protein) and high levels of large neutral aminoacids (LNAAs). In a recent study in 11 PKU patients it has been shown to be a safe and highly acceptable alternative to synthetic AAs. As an intact protein source, GMP improves protein retention and phenylalanine utilization compared with AAs [11].

LNAAs include tyrosine, tryptophan, threonine, methionine, valine, isoleucine, leucine, and histidine. Phe and LNAAs share the same transport system to enter the brain, so high LNAA concentrations may block the transport of Phe to the brain and then reduce brain Phe concentrations. They also share the same transport system to enter the blood system across the gut. Possible LNAA treatment targets include reduction of blood and brain Phe concentrations, augmentation of cerebral neurotransmitter synthesis, and/or elevation of brain non-Phe LNAA concentrations [12]. There is no adequate preparation for use in infants and young children. Its use can be considered in conjunction with moderate protein restriction in patients who have a lot of difficulty taking their medical food/formula.

Many individuals with primary PAH deficiency are responsive to BH4 (5–20 mg/kg daily in divided oral doses). The majority of individuals with mild or moderate PKU may be responsive to BH4 while up to 10% of individuals with classic PKU can show a response. BH4 enhances in vivo phenylalanine hydroxylation and lowers plasma phenylalanine concentration so patients can increase their intact protein intake. An orally active formulation of BH [4] (sapropterin dihydrochloride; Kuvan) is now commercially available. Clinical studies suggest that treatment with sapropterin provides better Phe control and increases dietary Phe tolerance, allowing significant relaxation, or even discontinuation, of dietary Phe restriction. Firstly, patients who may respond to this treatment need to be identified [13].

Tyrosinemia Type I

Tyrosine is a nonessential aromatic amino acid. It can be obtained from food, but it is also obtained from phenylalanine and from protein catabolism. Among other important functions, it is used in the synthesis of catecholamines, thyroid hormones, and melanin.

Deficiencies in the activity of tyrosine aminotransferase, the first enzyme in the catabolic pathway of tyrosine, result in tyrosinemia type II (OMIM 276600), an autosomal recessive disorder also known as Richner–Hanhart's syndrome.

At the end of the catabolic pathway, fumarylacetoacetic acid is metabolized to fumaric acid and acetoacetic acid by fumarylacetoacetate hydrolase. Deficiencies in this enzyme result in tyrosinemia type I (OMIM 276700), also inherited in an autosomal recessive manner.

Clinical symptoms in the early stages of the disease include vomiting, diarrhea, failure to thrive, and abdominal distension. Complications that may develop include hepatomegaly, splenomegaly, ascites, edema, and hemorrhagic tendencies.

The pathogenesis of tyrosinemia type I is complex and involves the following: depletion of glutathione, accumulation of succinylacetone, inhibition of certain enzymes (including one in the porphyrin pathway), eventual hepato-cellular degeneration, nodular cirrhosis, or hepatoma. Elevated serum alpha-fetoprotein is a marker of the hepatic complications. Renal complications include tubular reabsorption impairment and Fanconi's syndrome [14].

The use of the drug NTBC 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione inhibits the enzyme pHPPD (hydroxyphenylpyruvic acid dioxygenase), and prevents synthesis of fumarylacetoacetate and succinylacetone. Clinically, NTBC has been shown to prevent acute porphyric episodes, decrease the rate of progression of liver cirrhosis and Fanconi's syndrome and the need for liver transplantation [15]. On the other hand, its effects do not eliminate the risk for hepatocarcinoma present in these patients.

Liver transplantation has successfully improved the outcome for persons with tyrosinemia type I. Although long-term data on patients with liver transplants are not yet available, transplants seem to cure liver manifestations and prevent the development of hepatomas and further neurological crises.

Dietary Management of Tyrosinemia Type I

The goal of dietary management is to provide a diet restricted in both phenylalanine and tyrosine [16]. Adequate protein is provided through special formulas (medical foods) that do not contain phenylalanine, tyrosine, or methionine. Total phenylalanine and tyrosine should be restricted adequately so that blood tyrosine levels are between 30 and 100 mmol/L. For patients on NTBC therapy, nutrition management should maintain plasma tyrosine levels approximately <500 mmol/L.

When the diagnosis is made, all tyrosine and phenylalanine should be eliminated from the diet for up to 48 h. Specialized amino acid formulas are used to provide tyrosine and phenylalanine-free

protein, calories, vitamins, and minerals. Tyrosine and phenylalanine, from either breastmilk or regular infant formula, are gradually introduced. An adequate energy intake should be achieved in order to prevent catabolism and succinylacetone overproduction [17].

Tyrosinemia Type II

Tyrosinemia type II (also known as oculocutaneous tyrosinemia), tyrosine amino transferase deficiency, and Richner–Hanhart syndrome [18] are characterized by greatly elevated concentrations of blood and urine tyrosine and by increases in urinary phenolic acids, *N*-acetyltyrosine, and tyramine. Features of disease include eye, skin, and neurological signs.

Eye features include hyperlacrimation, photophobia, redness, and pain. Painful hyperkeratotic plaques occur on the soles of the feet and palms of the hands. Neurological abnormalities include mental retardation and, rarely, seizures. Dietary control may help improve the skin and eye lesions.

Dietary Management of Tyrosinemia Type II

The goals of dietary management are similar to type I tyrosinemia. Methionine restriction is not necessary. Special medical foods are available to provide adequate protein, vitamins, and minerals.

Phenylalanine and tyrosine are restricted so that tyrosine levels are maintained at approximately ~20 mg/dL [19]. Because this diagnosis is usually made later in life, instituting the diet may be difficult in a person who already has defined food likes and dislikes.

Homocystinuria

Elevated homocysteine may be caused by several different defects involving methionine metabolism. The most common inborn error in methionine metabolism is the deficiency of cystathionine b-synthase (OMIM 236200), a vitamin B6-dependent enzyme which converts homocysteine to cystathionine. Both homocysteine and methionine are elevated. Homocysteine may also be re-methylated back to methionine. The primary mode of re-methylation occurs through the transfer of a methyl group from N5-methyltetrahydrofolate to homocysteine. Cofactors for this reaction are B12 and folate dependent; abnormalities in the cofactors result in elevated homocysteine with normal methionine levels. Another re-methylation pathway uses betaine, which is derived from choline, as the methyl donor.

Patients with the classic form of homocystinuria who are untreated or poorly controlled develop clinical manifestations over time. These include dislocation of the ocular lens (ectopia lentis), skeletal malformations with Marfanoid features, mental retardation, and vascular complications involving atherosclerosis with a predisposition to thromboembolic events.

Dietary Management of Homocystinuria

About half of these deficiencies are responsive to vitamin B6. If reductions on plasma homocysteine and/or methionine levels 24 h after the administration of oral B6 doses (starting in 100 mg/dose, then next day 200 mg if no response until a maximum dose of 300 mg in infants or 500 mg in children) are greater than 30% from baseline levels, the patient is considered B6 responsive [20].

For patients who do not respond to B6 supplementation, a methionine-restricted diet is recommended, with a supplementation of cystine. Folic acid, vitamin B12, and betaine are usually used as coadjuvants. Dietary methionine should be restricted to levels that maintain adequate growth. Restriction may be achieved by either limiting methionine or limiting protein and supplementing with a methionine-free

metabolic formula. Cystine becomes a conditionally essential nutrient because its synthesis is impaired. Recommended intakes in infants in the first 3 months of life range from 15 to 60 mg/kg and from 85 to 150 mg/kg for methionine and cystine respectively [21].

Treatment that is started during infancy usually prevents the development of mental retardation and skeletal abnormalities. However, dislocation of the ocular lens is usually detected regardless of treatment, occurring by the fourth decade in nearly all treated patients [22]. Lifelong treatment is recommended to minimize the development of vascular complications.

Maple Syrup Urine Disease

Maple syrup urine disease (MSUD; branched-chain ketoaciduria, OMIM 24860) is an autosomal recessive disorder caused by a deficiency of the enzyme complex branched-chain alpha-ketoacid dehydrogenase. The enzyme is common to the degradative pathways of the branched-chain amino acids (BCAA)—leucine, valine, and isoleucine. Thiamine is the coenzyme. The block results in increased levels of the amino acids and their keto-derivatives in blood, urine, and cerebrospinal fluid. The accumulation and presence of alloisoleucine, the stereoisomer of isoleucine, is diagnostic of MSUD.

MSUD patients can be divided into five types based on their presentation and their response to thiamine. The five phenotypes are classic, intermediate, intermittent, thiamine-responsive, and dihydrolipoyl dehydrogenase (E3) deficient. Dihydrolipoyl dehydrogenase (E3) deficiency is extremely rare and mimics the clinical phenotype of intermittent MSUD with the additional feature of severe lactic acidosis. Attempts at treatment with protein restriction and vitamins (thiamine, biotin, and lipoic acid) have not yet been successful [23].

High levels of leucine and its ketoacid, alpha-ketoisocaproic acid, appear to be the neurotoxic agents in the disorder. Leucine levels tend to be more greatly elevated than the others and respond to dietary restriction more slowly because leucine is the predominant BCAA in most animal and plant proteins [24].

Classic MSUD is the most frequent form of presentation, accounting for approximately 80% of the cases. It usually presents in the first week of life with symptoms including feeding difficulties, lethargy, metabolic acidosis, and the distinctive maple syrup odor in the urine, sweat, and earwax. Neurological impairment may progress to seizures, apnea, and death within 10 days of life [25].

The intermediate and intermittent forms have an increased amount of functional enzyme. Patients with intermediate MSUD may have failure to thrive and developmental delay. Alloisoleucine, BCAA, and branched-chain keto acids (BCKA) are persistently elevated, but acidosis is uncommon. Patients with intermittent MSUD have normal BCAAs but become susceptible to elevated levels during periods of illness or stress. The features of thiamine-responsive MSUD are similar to the intermediate form. Pharmacological doses of thiamine (100–150 mg/day) along with a protein-restricted diet result in lowered amounts of BCAA and BCKA [26].

Dietary Management of Maple Syrup Urine Disease

Treatment involves both long-term dietary management and aggressive therapy during acute metabolic decomposition. Early diagnosis and initiation of a BCAA-free diet before the age of 10–14 days is essential to reduce the risk of permanent neurological damage or death.

The goal of acute therapy is to correct the acidosis and normalize the amino acid concentrations. Initial measures may include peritoneal dialysis, renal dialysis, or parenteral nutrition [27]. When the clinical status has stabilized, oral feedings using special formulas without BCAA are given.

Long-term dietary therapy requires the restriction of leucine, isoleucine, and valine so that only the amount necessary for normal growth and development is provided. Blood levels of amino acids (especially leucine) must be monitored. Because the leucine concentration of natural protein is greater

than isoleucine or valine concentrations, supplements of these two amino acids may be needed to maintain normal serum levels. Special BCAA-free formulas are required to fulfill the total protein requirements.

Organic Acidemias: Propionic Acidemia and Methylmalonic Acidemia

Propionic acidemia (PPA, OMIM 606054) and methylmalonic acidemia (MMA, OMIM 25100) are autosomal recessively inherited disorders and share similar metabolic pathways, clinical features, and treatment. Both disorders are due to defects in methionine, threonine, valine, isoleucine, odd-chain fatty acid, and eventually propionate metabolism. The metabolic defect occurs in the enzyme propionyl-CoA carboxylase or methylmalonyl-CoA mutase. Methylmalonyl-CoA mutase is vitamin B12 dependent, therefore poor activity may also be caused by defects in the formation of the B12 cofactor. Metabolic acidosis with hyperammonemia and ketonuria are features of episodic decompensation, usually precipitated by excessive protein intake, constipation, or infection.

They usually appear in the neonatal period as an "intoxication type" disease, with vomiting, lethargy, metabolic acidosis with increased anion gap, and coma. Untreated patients will often die or suffer from severe neurologic sequelae.

Hyperammonemia is a result of the abnormal organic acid, propionate (propionyl-CoA) or methylmalonate (methylmalonyl-CoA), which interfere with the urea cycle by inhibiting formation of *N*-acetylglutamate, the cofactor for carbamoyl phosphate synthetase, early in the urea cycle [28]. Hyperglycinemia is common and may be due to prolonged intake of excess protein or inhibited glycine cleavage due to isoleucine metabolites [29].

The exact mechanism of increased glycine is unknown. The organic acids identified in the urine include methylcitrate and 3-hydroxypropionate for PPA and methylmalonic acid for MMA.

Dietary Management

The goals of dietary therapy can be divided into acute episode management and long-term management. During the acute phase, the goals are to maintain biochemical balance by aggressively treating the ketoacidosis. Large amounts of fluid and protein-free calories (up to 50% above normal intake) are given either internally if tolerated or intravenously. Sodium bicarbonate may also be required to treat the acidosis.

Long-term management aims to prevent ketoacidosis and reduce accumulation of the metabolites. Protein intake from natural sources should be restricted to approximately 50% of the recommended amount for age. However, natural protein tolerance is highly individual and requires frequent monitoring of urine organic acids and ketones, as well as of blood amino acids and ammonia. Amino acid supplementation, in the form of both a metabolic formula and individual amino acids, is usually required.

Odd-chain fatty acid metabolism is also impaired in both disorders. Dietary sources of these fatty acids as butter or cream should be avoided in these patients. Fasting should also be avoided because of induction of catabolism and endogenous odd-chain fatty acid production [30].

Nutritional management may be complicated by food refusal, apparent lack of appetite, and frequent vomiting. Aggressive nutrition support (i.e., feeding tube) should be considered if an adequate nutrient intake cannot be achieved with oral feedings.

Some cases of MMA respond to therapeutic doses of vitamin B12, which is a component of a coenzyme required for the conversion of methylmalonyl-CoA to succinyl-CoA. Carnitine supplementation is also recommended.

Urea Cycle Defects

In the urea cycle, five enzymes (carbamoyl phosphate synthase, ornithine transcarbamylase, argininosuccinate synthetase, argininosuccinate lyase, and arginase) and a producer of an allosteric activator (*N*-acetyl glutamate synthetase) are involved This metabolic pathway is responsible for converting ammonia to urea. If a deficiency occurs in anyone of the enzymes, ammonia accumulates in the blood and all the cells of the body. All of the six enzymes mentioned has a known defect. Ornithine transcarbamylase deficiency is inherited as an X-linked disease, but the rest are AR.

Neonatal screening is not available for all the enzyme defects involved in the urea cycle. Clinical signs and symptoms may appear anytime from the neonatal period to adulthood depending on the defective enzyme and the severity of the deficit. The clinical signs include poor feeding, vomiting, lethargy, hypotonia, stupor and bleeding diatheses, convulsions, coma, shock, and death. Infection or increased protein intake often precede development of clinical features. Infants who survive the adverse effects of elevated ammonia are often mentally retarded. However, successful control of the metabolic crisis and prevention of the prolonged hyperammonemia may prevent the adverse outcome during the neonatal period [31]. Besides the neonatal period, there are other ages when symptoms are likely to occur. These include later in infancy when high-protein formula or milk is introduced, during infection and during puberty (possibly caused by lowered compliance to diet or medication) [32].

Plasma ammonia levels in the healthy infant are usually less than 50 mmol/L. Generally a plasma ammonia concentration over 150 mmol/L is observed in these disorders in the acutely ill patient.

Dietary Management of Urea Cycle Disorders

The goal of dietary management is control of blood ammonia levels with a maintenance of adequate plasma concentrations of amino acids. This is accomplished with a combination of protein restriction, supplementation with individual amino acids (arginine and citrulline), and use of medication (sodium benzoate or phenylbutyrate) to help decrease accumulated nitrogenous metabolites by providing alternate pathways for nitrogen excretion [33].

Typical diets will consist of 1–1.5 g protein/kg/day during the first few years of life. Intact protein from proprietary formula in infants and from sources like fruits, vegetables, and grains in older children may represent up to 50% of the daily protein intake. The use of an essential amino acid modified formula may be beneficial for maintaining adequate plasma amino acid levels while on a protein-restricted diet [34]. Energy intake should be enough to prevent catabolism without promoting excessive weight gain and obesity.

Specific instructions should be given to the caregivers in the case of acute illness or physical trauma. If patient develops hyperammonemia, treatment is urgent, and a complete protein restriction should be started. A high energy nutritional support should also be given, either orally or I.V. 48–72 h after starting the therapy, protein should be reintroduced in the diet in order to prevent protein catabolism. Sodium benzoate and phenylbutyrate are also used to help as nitrogen scavengers. Arginine supplementation is also needed to enhance nitrogen excretion. If hyperammonemia cannot be controlled, dialysis should be started.

Fatty Acid Oxidation Defects

Fatty acid oxidation defects are inborn errors of fat metabolism. There are currently at least 22 known defects. Common features include acute metabolic decompensation associated with fasting, hypoketotic

hypoglycemia, involvement of cardiac or skeletal muscle, and alterations of plasma or tissue carnitine. The disorders may be divided into categories of transport defects and disorders of the beta-oxidation pathway.

Transport defects include carnitine uptake deficiency, carnitine palmitoyl transferase deficiency (CPT I), CPT II, and translocase deficiency (Trans). These enzymes are involved with transporting fatty acids from the cytoplasm into the mitochondria.

Disorders of beta-oxidation include long-chain acyl-CoA dehydrogenase, medium-chain acyl-CoA dehydrogenase (MCAD), short-chain acyl-CoA dehydrogenase, long-chain 3-hydroxyacyl-CoA dehydrogenase, and short-chain 3-hydroxyacyl-CoA dehydrogenase. MCAD deficiency is the most common disorder of fatty acid oxidation and has been associated with sudden infant death syndrome [35].

Neonatal screening with tandem mass spectroscopy can detect these disorders based on their specific blood acylcarnitine profile. Neonatal detection of this illnesses is crucial. If untreated, up to one-third of the initial episodes observed could be fatal.

The primary treatment for all the disorders is to avoid prolonged fasting. In general, recent guidelines recommend the following approach: infants up to 4 months of age should not fast for more than 4 h. Until the first year of age, an additional hour of fasting can be added for each month. After that age, fasting for more than 12 h should be avoided [36]. Uncooked cornstarch (UCS) has been used to help delay the onset of fasting. The prescribed dose (usually 1.5–2 g/kg body weight) may be added to formula at night.

Blood glucose concentrations are a poor indicator of metabolic status in these patients. In a study performed in the Netherlands in 6 of 35 patients who underwent a fasting test, clinical symptoms appeared before hypoglycemia developed [37].

Because fatty acids become available when fat stores are mobilized or when dietary fat is consumed, dietary fat restriction may be beneficial. Long-chain fats are often limited to 10–20% of total calories. Linoleic and linolenic acid should provide 3 and 0.5% respectively of total daily calories [38]. Medium-chain triglyceride oil may be a useful adjunct calorie source in defects involving long-chain fatty acids. Care should be taken to avoid excess calorie intake, which would lead to storage as long-chain fats in the adipose tissue.

Disorders of Carbohydrate Metabolism

Galactosemia

Galactosemia (OMIM 230400) may be caused by a defect in one of three different enzymes necessary for galactose metabolism. A deficiency of galactose-I-phosphate uridyl transferase activity results in the most common form of galactosemia.

Galactose, galactitol, and galactose-1-phosphate accumulate in blood and tissues. Early features of untreated galactosemia appear in infancy and include hypoglycemia, jaundice, failure to thrive, vomiting, and *Escherichia coli* sepsis. The symptoms appear after an infant has begun consuming milk sugar from formula or breast milk. Without treatment, death from *E. coli* sepsis of meningitis occurs within the first 1–2 weeks of life [39]. If the infant survives, long-term features of the disease include mental retardation, liver cirrhosis, and cataracts.

Early detection and elimination of galactose from the diet can prevent death and reduce the risk of cataracts. Many states include galactosemia in their newborn screening programs. However, dietary treatment does not seem to guarantee a normal clinical outcome. Neurological impairment and suboptimal intellectual development has been reported [40]. Most females have ovarian failure [41]. The reason for these poor outcomes has not been definitively determined. Theories include fetal damage in utero or before intervention, endogeneous production of galactose [42], or inadequate or excess galactose intake.

Dietary Management of Galactosemia

A galactose-restricted diet should begin as soon as the infant is diagnosed. Soy formula should replace cow's-milk based formulas or human milk. It should be noted that starch components of soy in soy formula naturally contain some galactose. However, the enzyme a-galactosidase, required to release the galactose from the soy, is not found in humans. Generally, milk-free foods form the base of the diet. Hidden sources of lactose must also be avoided. This is accomplished by reading labels and avoiding ingredients such as whey, casein, nonfat dry milk, milk solids, lactose, hydrolysed protein, lactoglobulin, lactalbumin, caseinate, and soy flour. Organ meats must be avoided because they are a storage site for galactose.

Given the poor outcome even among those patients that are compliant with the traditional diet, it has been suggested that additional sources of galactose, more recently discovered, may be resulting in a chronic galactose intake. These foods include several fruits, vegetables, legumes, nuts, and cereals [43].

The effect of dietary restriction can be monitored by measuring the postprandial erythrocyte GAL-1-P concentration or filter paper whole blood samples. A well-treated patient should maintain levels <3.0 mg/dL [44].

Glycogen Storage Disease

At least 12 different types of glycogen storage diseases (GSD) have been identified. Abnormalities of the biochemical pathways involved in glycogenolysis and glycogen synthesis result in deposition of excess glycogen, abnormal structure of the compound, or both. The liver and muscle are the major sites of glycogen deposition. Common signs and symptoms include hypoglycemia, hepatomegaly, muscle weakness, and cramping and fatigue. This section focuses on the type of GSD that respond to nutritional therapy.

GSD Ia (von Gierke's Disease)

GSD la results from a deficiency of glucose-6-phosphatase, the last enzyme in the pathways involved in the production of glucose from either gluconeogenesis or glycogenolysis. GSD lb, a clinical variant of la, results from a defect in the glucose-6-phosphate transport protein and responds to the same nutritional intervention as does Ia. Biochemical abnormalities seen in GSD I include lactic acidemia, hypoglycemia, hyperlipidemia, and hyperuricemia.

Dietary Management for GSD Ia

Because endogenous glucose production is limited, a constant source of exogenous glucose is necessary to maintain a normal plasma glucose concentration and prevent hypoglycemia. Historically, treatment for hypoglycemia included portacaval shunts and total parenteral nutrition [45] or continuous enteral tube feedings [46, 47].

More recently, UCS [48, 49] has been widely used to provide a source of continuous glucose. UCS is effective in maintaining normoglycemia and improving metabolic abnormalities [50] and growth retardation [51]. Side effects may include diarrhea and flatulence until acclimated to the cornstarch and excessive weight gain [48]. Continuous nocturnal tube feedings of glucose and intermittent doses of UCS are the two dietary manipulations most commonly used to manage GSD I.

Pancreatic amylase activity is insufficient in infants younger than 12 months. UCS could be safely started beyond that age point. Anyway, UCS can be started before cautiously, at a starting dose of 0.25 g/kg. This dose is increased gradually in order to prevent side effects as bowel distention, loose stools, and flatulence. Doses are given at 3–5 h intervals during the day and 4–5 h intervals at night [52]. As the child grows, UCS is given at longer periods reaching a 6 h interval and a 1.5–2 g/kg in adolescents [53]. The dose and schedule may be adjusted according to blood glucose monitoring results.

UCS can be mixed with water at a starch/water ratio of 1:2, and glucose or sucrose addition to the mixture is contraindicated, to avoid insulin release. Mixing the UCS with milk or yogurt is also possible without affecting the glycemic control.

Infants should be fed every 2–4 h with a glucose-containing formula. Tube feedings of the same formula are often necessary, later in infancy, to ensure normoglycemia, particularly at night [54, 55]. Alternatively, nocturnal nasogastric or gastrostomy feedings may be used to provide adequate glucose during an overnight fast combined with frequent daytime oral feedings [47, 56]. The formula should contain the minimum dose of glucose necessary to maintain blood glucose levels. Although proven effective, tube feedings also pose significant risk of hypoglycemia in the case of pump malfunction or other case of interrupted feeding [57]. Patients should eat immediately after the overnight feeding has been discontinued.

The diet usually contains 60–70% of calories as carbohydrate (the majority of which is complex), 20% as fat, and the remainder as protein. Because patients are unable to metabolize either galactose or fructose the diet should be limited in dairy products, fruits, and simple carbohydrates. However universal agreement on the degree of limitation has not been reached [58]. Dietary restrictions are likely to necessitate the use of multivitamins and calcium supplements.

Dietary Management for GSD IV

Liver transplant is the only present effective treatment. Dietary therapy is indicated to prevent hypoglycemia and to improve growth and muscle strength prior to transplant [59].

GSD III (Debrancher deficiency; Limit dextrinosis; Cori or Forbes disease).

Patients with GSD III are able to degrade glycogen only partially due to a deficiency of amylo-1,6-glucosidase enzyme activity. This enzymatic deficiency results in the accumulation of abnormal glycogen in the liver. Unlike GSD I, these patients are able to synthesize glucose via gluconeogenesis. The clinical characteristics are similar to GSD I with distinguishing features including fasting ketosis, less significant hypoglycemia and hyperlipidemia and absence of lactic acidemia and hyperuricemia.

Dietary Management for GSD III

Dietary treatment is less demanding than in GSD type Ia [60]. Sucrose, fructose, and lactose are not restricted. Frequent daytime meals and snacks are recommended to maintain normoglycemia. As in GSD I, either UCS [61] or nocturnal tube feedings [62] is recommended to prevent hypoglycemia during the night.

A high-protein diet to provide increased substrate for gluconeogenesis has been advocated to help reverse myopathy and prevent growth retardation. A diet consisting of 20–25% protein with approximately one-quarter to one-third given as a high-protein nocturnal tube feeding reversed myopathy in GSD III patients with severe muscle wasting disease [63].

No nutritional therapies are either known or indicated for GSD types II, V, VII, or X [64].

Discussion

The treatment of many inborn errors of metabolism is often nutritional, involving alterations in protein, carbohydrate, fat, or energy intake. Dietary manipulations should be undertaken with a physician who is familiar with the disorders and an experienced dietician. The goal should be not only to prevent adverse outcomes but also to assist families and patients to incorporate their special diets into a lifestyle that is as normal and as healthy as possible.

References

1. Bernard M, Furuta L, Lo C. Nutritional support in inborn errors of metabolism. In: Preedy VR, George G, Ronald W, editors. Nutrition in the infant: problems and practical procedures. Cambridge: Cambridge University Press; 2001. p. 361–78.
2. Bickel H, et al. The influence of phenylalanine intake on the chemistry and behavior of a phenylketonuric child. Lancet. 1953;2:812–3.
3. Mitchell JJ, Scriver CR. Phenylalanine hydroxylase deficiency. 2000 Jan 10 [updated 2010 May 4]. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993. http://www.ncbi.nlm.nih.gov/books/NBK1504/.
4. Hackney IM, et al. Phenylketonuria: mental development, behavior, and termination of low phenylalanine diet. Pediatrics. 1968;72:646–55.
5. Guldberg P, Rey F, Zschocke J, Romano V, François B, Michiels L, Ullrich K, Hoffmann GF, Burgard P, Schmidt H, Meli C, Riva E, Dianzani I, Ponzone A, Rey J, Güttler F. A European multicenter study of phenylalanine hydroxylase deficiency: classification of 105 mutations and a general system for genotype-based prediction of metabolic phenotype. Am J Hum Genet. 1998;63:71–9.
6. Kaufman S. Unsolved problems in diagnosis and therapy of hvperphenylalaninemia caused by detects in tetrahydrobiopterin metabolism. J Pediatr. 1986;109:572–8.
7. Cockburn E, et al. Recommendation on the dietary management of phenylketonuria-Report of Medical Research Council Working Party on Phenylketonuria. Arch Dis Child. 1993;68:426–7.
8. Schuett VE. Low protein food list for PKU. 2nd ed. Burnaby: Hemlock Printers Ltd.; 2002.
9. Koch R, et al. The effect of diet discontinuation in children with phenylketonuria. Eur J Pediatr. 1987;146 Suppl 1:A12–A6.
10. Potocnik U, Widhalm K. Long-term follow-up of children with classical phenylketonuria after diet discontinuation: a review. J Am Coll Nutr. 1994;13:232–6.
11. van Calcar SC, MacLeod EL, Gleason ST, Etzel MR, Clayton MK, Wolff JA, Ney DM. Improved nutritional management of phenylketonuria by using a diet containing glycomacropeptide compared with amino acids. Am J Clin Nutr. 2009;89:1068–77.
12. van Spronsen FJ, de Groot MJ, Hoeksma M, Reijngoud DJ, van Rijn M. Large neutral amino acids in the treatment of PKU: from theory to practice. J Inherit Metab Dis. 2010;33:671–6.
13. Blau N, Bélanger-Quintana A, Demirkol M, Feillet F, Giovannini M, MacDonald A, Trefz FK, van Spronsen FJ. Optimizing the use of sapropterin (BH(4)) in the management of phenylketonuria. Mol Genet Metab. 2009;96:158–63.
14. Kvittingen EA. Hereditary tyrosinemia type I: an overview. Scand J Clin Lab Invest. 1986;46(Suppl184):27–34.
15. Masurel-Paulet A, Poggi-Bach J, Rolland MO, Bernard O, Guffon N, Dobbelaere D, Sarles J, de Baulny HO, Touati G. NTBC treatment in tyrosinaemia type I: long-term outcome in French patients. J Inherit Metab Dis. 2008;31:81–7.
16. Holme E, Lindstedt S. Nontransplant treatment of tyrosinemia. Clin Liver Dis. 2000;4:805–14.
17. Acosta PB, Matalon KM. Nutrition management of patients with inherited disorders of aromatic amino acid metabolism. In: Acosta PB, editor. Nutrition management of patients with inherited metabolic disorders. Sudbury, MA: Jones and Bartlett publishers; 2010. p. 119–74.
18. Mitchell GA, Grompe M, Lambert M, Tanguay RM. Hypertyrosinemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular bases of inherited disease. 8th ed. New York: McGraw-Hill; 2001. p. 1777–805.
19. Ney D, et al. Dietary management of oculocutaneous tyrosinemia in an 11-year-old child. Am J Dis Child. 1983;137:995–1000.

20. Mudd SH, Levy HL, Kraus JP. Disorders of transsulfuration. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular basis of inherited disease. New York: McGraw-Hill; 2001. p. 2007–56.
21. van Calcar S. Nutrition management of patients with inherited disorders of sulfur amino acid metabolism. In: Acosta PB, editor. Nutrition management of patients with inherited metabolic disorders. Sudbury, MA: Jones and Bartlett publishers; 2010. p. 237–81.
22. Andria G, Sebastio G. Inborn metabolic diseases—diagnosis and treatment. Berlin: Springer; 1996.
23. Chuang DT, Shih VE. Maple syrup urine disease (branched-chain ketoaciduria). In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular bases of inherited disease. 8th ed. New York: McGraw-Hill; 2001. p. 1971–2005.
24. Berry GT, et al. Branched-chain amino acid-free parenteral nutrition in the treatment of acute metabolic decompensation in patients with maple syrup urine disease. N Engl J Med. 1991;324:175–9.
25. Simon E, Flaschker N, Schadewaldt P, Langenbeck U, Wendel U. Variant maple syrup urine disease (MSUD)–the entire spectrum. J Inherit Metab Dis. 2006;29:716–24.
26. Duran M, Wadman SK. Thiamine-responsive inborn errors of metabolism. J Inherit Metab Dis. 1985;8 Suppl 1:70–5.
27. Jouvet P, Jugie M, Rabier D, Desgrès J, Hubert P, Saudubray JM, Man NK. Combined nutritional support and continuous extracorporeal removal therapy in the severe acute phase of maple syrup urine disease. Intensive Care Med. 2001;27:1798–806.
28. Petrowski S, et al. Pharmacologic amino acid acylation in the acute hyperammonemia of propionic acidemia. J Neurogenet. 1987;4:87–96.
29. Hillman RE, et al. Inhibition of glycine oxidation in cultured fibroblasts by isoleucine. Pediatr Res. 1973;7:945–7.
30. Yannicelli S. Nutrition management of patients with inherited disorders of organic acid metabolism. In: Acosta PB, editor. Nutrition management of patients with inherited metabolic disorders. Sudbury, MA: Jones and Bartlett publishers; 2010. p. 283–341.
31. Maestri NE, et al. Prospective treatment of urea cycle disorders. J Pediatr. 1991;119:923–8.
32. Treem WR. Inherited and acquired syndromes of hyperammonemia and encephalopathy in children. Semin Liver Dis. 1994;14:236–57.
33. Brusilow SW, Horwich AL. Urea cycle enzymes. In: Scriver CS, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular basis of inherited disease. 8th ed. New York: McGraw-Hill; 2001. p. 1909–63.
34. Singh RH, Rhead WJ, Smith W, Lee B, Sniderman King L, Summar M. Nutritional management of urea cycle disorders. Crit Care Clin. 2005;21(Suppl):S27–35.
35. Brackett J-C, et al. A novel mutation in medium chain acyl-CoA dehydrogenase causes sudden neonatal death. J Clin Invest. 1994;94:1477–83.
36. Gillingham MB. Nutrition management of patients with inherited disorders of mitochondrial fatty acid oxidation. In: Acosta PB, editor. Nutrition management of patients with inherited metabolic disorders. Sudbury, MA: Jones and Bartlett publishers; 2010. p. 369–403.
37. Derks TG, van Spronsen FJ, Rake JP, van der Hilst CS, Span MM, Smit GP. Safe and unsafe duration of fasting for children with MCAD deficiency. Eur J Pediatr. 2007;166:5–11.
38. Acosta PB, Yanicelli S. The ross metabolic formula system nutrition support protocols. 4th ed. Columbus: Ross Products Division/Abbott Laboratories; 2001.
39. Elsas LJ, et al. Galactosemia: a molecular approach to the enigma. Int Pediatr. 1993;8:101–9.
40. Fishler K, et al. Intellectual and personality development in children with galactosemia. Pediatrics. 1972;50:412–9.
41. Kaufman FR, Kogut MD, Donnell GN, Goebelsmann U, March C, Koch R. Hypergonadotropic hypogonadism in female patients with galactosemia. N Engl J Med. 1981;304:994–8.
42. Berry GT, et al. Endogenous synthesis of galactose in normal men and patients with hereditary galactosaemia. Lancet. 1995;346:1073–4.
43. Acosta PB, Gross KC. Hidden sources of galactose in the environment. Eur J Pediatr. 1995;154 Suppl 2: S87–92.
44. Wenz E. Pediatric nutrition in chronic diseases and developmental disorders. New York: Oxford University Press; 1993.
45. Folkman J, Philippart A, Tze WJ, Crigler J. Portacaval shunt for glycogen storage disease: value of prolonged intravenous hyperalimentation before surgery. Surgery. 1972;72:306–14.
46. Burr IM, O'Neill JA, Karzon DT, Howard LJ, Greene HL. Comparison of the effects of total parenteral nutrition, continuous intragastric feeding, and portacaval shunt on a patient with type I glycogen storage disease. J Pediatr. 1974;85:792–5.
47. Greene HL, Slonim AE, Burr IM, Moran JR. Type I glycogen storage disease: five years of management with nocturnal intragastric feeding. J Pediatr. 1980;96:590–5.

48. Chen YT, Bazzarre CH, Lee MM, Sidbury JB, Coleman RA. Type I glycogen storage disease: nine years of management with cornstarch. Eur J Pediatr. 1993;152 Suppl 1:S56–S9.
49. Chen YT, Cornblath M, Sidbury JB. Cornstarch therapy in type I glycogen-storage disease. N Engl J Med. 1984;310:171–5.
50. Wolfsdorf JI, Rudlin CR, Crigler JF. Physical growth and development of children with type I glycogen- storage disease: Comparison of the effects of long-term use of dextrose and uncooked cornstarch. Am J Clin Nutr. 1990;52:1051–7.
51. Wolfsdorf JI, Keller RJ, Landy H, Crigler JE. Glucose therapy for glycogenosis type I infants: comparison of intermittent uncooked cornstarch and continuous overnight glucose feedings. J Pediatr. 1990;117:384–91.
52. Wolfsdorf JI, Crigler JE. Glycogen storage diseases. In: Lavin N, editor. Manual of endocrinology and metabolism 37. 2nd ed. Boston: Little, Brown and Company; 1994. p. 505–16.
53. Rake JP, Visser G, Labrune P, Leonard JV, Ullrich K, Smit GP, European Study on Glycogen Storage Disease Type I (ESGSD I). Guidelines for management of glycogen storage disease type I—European Study on Glycogen Storage Disease Type I (ESGSD I). Eur J Pediatr. 2002;161 Suppl 1:S112–S9.
54. Fernandes J, Leonard JV, Moses SW, Odievre M, di Rocco M, Schaub J, Smit GPA, Ullrich K, Durand P. Glycogen storage disease: recommendations for treatment. Eur J Pediatr. 1988;147:226–8.
55. Wolfsdorf JI, Plotkin RA, Laffel LMB, Crigler JE. Continuous glucose for treatment of patients with type I glycogen-storage disease: Comparison of the effects of dextrose and uncooked cornstarch on biochemical variables. Am J Clin Nutr. 1990;52:1943–50.
56. Greene HL, Slonim AE, O'Neill JA, Burr IM. Continuous nocturnal intragastric feeding for management of type I glycogen-storage disease. N Engl J Med. 1976;294:423–5.
57. Leonard JV, Dunger DB. Hypoglycaemia complicating feeding regimens for glycogen-storage disease. Lancet. 1978;2:1203–4.
58. Goldberg T, Slonim AE. Nutrition therapy for hepatic glycogen storage diseases. J Am Diet Assoc. 1993;93:1423–30.
59. Greene HL, Ghishan EK, Brown B, McClenathan DT, Freese D. Hypoglycemia in type IV g1ycogenosis: hepatic improvement in two patients with nutritional management. J Pediatr. 1988;112:55–8.
60. Kishnani PS, Austin SL, Arn P, Bali DS, Boney A, Case LE, Chung WK, Desai DM, El-Gharbawy A, Haller R, Smit GP, Smith AD, Hobson-Webb LD, Wechsler SB, Weinstein DA, Watson MS, ACMG. Glycogen storage disease type III diagnosis and management guidelines. Genet Med. 2010;12:446–63.
61. Gremse DA, Bucuralas JC, Batistreri WE. Efficacy of cornstarch therapy in type III glycogen storage disease. Am J Clin Nutr. 1990;52:671–4.
62. Borowitz SM, Greene HL. Cornstarch therapy in a patient with type III glycogen storage disease. J Pediatr Gastroenterol Nutr. 1987;6:631–4.
63. Slonim AE, Coleman RA, Moses WS. Myopathy and growth failure in debrancher enzyme deficiency: Improvement with high-protein nocturnal enteral therapy. J Pediatr. 1984;105:906–11.
64. Heller S, Worona L, Consuelo A. Nutritional therapy for glycogen storage diseases. J Pediatr Gastroenterol Nutr. 2008;47 Suppl 1:S15–21.

Chapter 3
Ketogenic Diet as Treatment Option for Infants with Intractable Epileptic Syndromes

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Key Points

- The ketogenic diet is an accepted treatment option in infants and young children with intractable epilepsy when antiepileptic drugs (AEDs) fail.
- The ketogenic diet is safe and effective in children with intractable epilepsy.
- Newly developed ketogenic diet formulas and special ketogenic calculating programs make a ketogenic diet easier to apply in daily practice even for infants and young children. It is possible to create age-appropriate schedules based on an individual's developmental stage or situation.

Keywords Infants • Infantile spasms • West syndrome • Refractory epilepsy • Catastrophic epileptic syndromes • Child • Treatment • Ketogenic diet • Pharmacologic treatment • Nonpharmacologic treatment

Introduction

A special diet for those suffering from epilepsy such as the ketogenic diet (KD) is a successful alternative treatment option in young children when treatment with different combinations of anti epileptic drugs (AEDs) fails.

Catastrophic epilepsy syndromes of early childhood, such as West and Ohtahara syndrome, are very difficult to treat (Table 3.1); they are associated with significant morbidity and mortality. Despite aggressive and early treatment, the outcome of these syndromes remains poor.

Infantile spasms (ISs) in neonates (Ohtahara syndrome) or infants (West syndrome) are one of the epilepsy syndromes seen in very young children with heterogeneous underlying causes (Table 3.2).

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Table 3.1 Epilepsy syndromes and incidence in children <12 months [9, 16, 26]

Epileptic syndrome	Incidence	Age of onset	Treatment options
Ohtahara	1:2,000	10 days–1 month	ACTH
West syndrome	1: 2,000	3–10 months	ACTH Vigabatrin Valproicacid corticosteroids Ketogenic diet Epileptic surgery
Symptomatic			
Crytptogenic			
Ideopathic			

ACTH adeno corticotropic hormone

Table 3.2 Common causes of infantile spasms [9]

In alphabetic order
Aicardi syndrome
Cytomegalovirus (CMV) infection
Down syndrome (trisomy 21)
Hemimegalencephaly
Hypoxic-ischemic encephalopathy
Incontinentia pigment
Intercranial hemorrhage
Lissencephaly
Sturge—Weber syndrome
Tuberous sclerosis complex (TSC)

Table 3.3 Treatment options of intractable epilepsy in children [1, 9, 26–28]

Pharmacologic	Nonpharmacologic
Antiepileptic drugs	Ketogenic diet
Monotherapy	
Cocktail multiple AED	
Pyridoxine (B6)	Vagus nerve stimulation
	Epileptic surgery

Accurate diagnosis and timely successful treatment can alter the disease course, especially in regard to the developmental delay and mental retardation that are hallmarks of this syndrome. Initial pharmacological treatment of ISs with AEDs often progresses to multiple drug regimes. A combination of drug and nonpharmacologic therapy or nonpharmacologic monotherapy is often used (Table 3.3) [1].

Commonly used treatment protocols in IS are based primarily on outcomes of studies on the efficacy and safety of pharmacological treatment with vigabatrine and corticosteroids (prednisolone or tetracosactide).

Studies on the efficacy and safety of nonpharmacologic treatment options in IS are scarce. In particular, prospective study designs are lacking. Despite this lack of evidence, an increasing number of studies are being conducted in an effort to obtain a favorable outcome.

Recent treatment protocols of IS also define nonpharmacologic treatment options when AEDs fail, but detailed information about the effects in infants is still lacking.

In this chapter we review the literature on the present status of the KD as a nonpharmacologic treatment option in IS.

The aim of this chapter is to show how a KD can be applied in infants with IS.

Background of the Ketogenic Diet in the Treatment of Epilepsy

In 1921 Dr. Rawle Geyelin in the USA discovered that the biochemical state of fasting caused a decrease in the occurrence of seizures. The production of ketone bodies was believed to be responsible for this and to be provoked by diets very high in fat, a KD [2]. Since that time the KD has become an important and successful treatment in intractable epilepsy. However, the popularity of the KD in medical use varied over the years.

When new AEDs were discovered, the KD became a "last resort" and was only used in cases where the epilepsy did not respond to drugs. The KD was found by children and their parents to be very rigid and difficult to apply due to the way in which it differ significantly from normal eating patterns (Table 3.4).

Only a few clinics kept using the KD on a regular basis. The John Hopkins University Hospital in Baltimore, MD, was one of those clinics that played an important role in the establishment of the KD. The Hopkins ketogenic diet protocol became well known and widely used for KD initiation [3].

In general there are two main versions of the KD : the classic version and the medium-chain-triglyceride (MCT) version. Differences in diet composition are shown in Table 3.5.

The classic version contains mainly long-chain triglycerides (LCTs). LCTs reach the liver in a roundabout way because they are first absorbed in the lymph system. This system requires carnitine for the transport of LCTs into the mitochondria, where β (beta) oxidation and ketone body synthesis take place.

In the case of the classic version of the KD, a certain ketogenic ratio (3:1, 4:1) is required to ensure an adequate production of ketone bodies.

General practice shows that special KD formulas (Ketocal® 4:1 or 3:1), based on the classic version of the KD, are well tolerated by infants.

The other version, a more liberal variant of the KD, is based on the use of MCTs. The mechanism on which the production of ketones in the use of MCTs is based involves a combination of rapid transport directly via the bloodstream and portal vein to the liver, after which MCTs are immediately metabolized by means of rapid absorption by the liver. This system does not require carnitine for MCT

Table 3.4 Diet composition [7, 8]

Subject	Normal diet	Ketogenic diet
Kcal	RDA[a]	RDA[a]
Fat (energy %)	30–35	70–90
Carbohydrate (energy %)	55–60	5–19
Protein (energy %)	5–10	5–11
Fluid	RDA	RDA
Supplements	No	Yes
Ketone bodies	No	Yes

[a]Recommended daily allowance

Table 3.5 Diet composition of ketogenic diets [7, 8]

Subject	Classical ketogenic diet	MCT version ketogenic diet	MCT/LCT combination version
Kcal	RDA	RDA	RDA
Fat (energy %)			
Total	90	71	75
LCT	90	11	25
MCT	–	60	50
Ratio[a]	4:1, 3:1	–	–
Carbohydrate (energy %)	5	19	15
Protein (energy %)	5	10	10

[a]Ratio = grams total fat: grams of protein and carbohydrate. (4:1 = 4 g fat vs. 1 g carbohydrate + protein)

Table 3.6 Adverse effects of ketogenic diet [7, 8]

Short term	Long term
Gastrointestinal	
Constipation	Growth retardation
Diarrhea	Kidney stones
Vomiting	
Abdominal pain	Osteoporosis
Metabolic abnormalities	Carnitine deficiency
Hyperlipidemia (cholesterol, triglycerides)	
Hyperurcemia	
Hypercalcemia	
Hypermagnesemia	
Decreased amino acid levels	
Acidosis	
Cardiac abnormalities	
Cardiomyopathy	
Prolonged QT interval	
Others	
Lethargy	
Hunger	

transport to the mitochondria. This increased ketogenic potential of MCTs means that less fat needs to be incorporated into the diet to ensure an adequate level of ketosis. In general practice, this means that more carbohydrates can be used, and this makes the diet more palatable and fosters compliance.

In practice, a third version of the diet exists: an MCT/LCT combined version with an adapted amount of MCT. This version was developed because some children, primarily the youngest, cannot easily tolerate the large quantity of MCT in the MCT version of the KD. Gastrointestinal complaints like diarrhea and abdominal discomfort are frequently seen in the very young when large amounts of MCT are used.

A Cochrane Review on KD for epilepsy in 2003 [4] showed no level-one evidence that supported the efficacy of the KD in epilepsy. Despite this fact, most retrospective data of the 20 studies and 956 patients strongly suggested that the KD could indeed be an important treatment option for epilepsy when multiple drugs failed.

An updated Cochrane Review on ketogenic diet for epilepsy in 2012 [5] included data form 4 randomized controlled trials. These studies recruited 289 children and adolescents. Although meta-analysis could not be done due to the heterogenity of the studies, the authors suggest that in children the KD results in short to medium term benefits in seizure control.

The underlying mechanism of the KD and its effect on seizures has been the subject of many studies but remains unidentified.

In 2008 [6] a large randomized controlled trial of 145 children, 2–16 years of age, with intractable epilepsy confirmed the efficacy of the KD, and its place as a treatment option was established. In this study children were randomly assigned to receive a KD (classic or MCT) either immediately or after a 3-month delay, with no other changes to treatment (control group). The two groups were compared for the effect on seizures of diet. With 3-, 6- and 12-month treatment durations, there were no significant differences in mean percentage of baseline seizures ($p > 0.05$ at all dates) between the two types of KD.

In this study, no significant differences in tolerability of the KD were found except that the classic group reported an increase in a lack of energy after 3 months and vomiting at 12 months. The outcomes showed both versions of the KD as being equally effective. Side effects could be treated by adjustments to the diet.

Using the KD may lead to side effects, which must be monitored carefully.

Attendance by a professional multidisciplinary team of a pediatric neurologist, pediatric dietitian, specialized nurse, and pediatrician is necessary (Table 3.6).

The aim of an international consensus statement is to advise on the optimal clinical management of children receiving the KD [7].

In the Netherlands, a Dutch Dietary Treatment Guideline for the KD in epilepsy treatment has been published [8]. It offers practical tools for successful diet calculation, diet initiation, and diet monitoring.

The availability of treatment guidelines will lead to increased safety and efficacy of the KD. The recommendations were as evidence based as possible.

Treatment Modalities in Infantile Spasms

Infantile Spasms

Although ISs are not rare, they are often only diagnosed after days or some weeks of spasms. The syndrome was first described in 1841 by Dr. William James West in an article in *the Lancet* regarding his own son. Since that time many efforts have been made to find the strongest evidence of several treatment options in IS. However the outcome is still poor [9].

Pharmacological Treatment

Antiepileptic Drugs

A recent Cochrane Review on the treatment of ISs [10], based on strict inclusion criteria, analyzed a limited number of 14 studies with 681 patients. The strongest evidence suggested that hormonal (prednisolone or tetracosactide) treatment led to resolution of spasms faster, and in more children, than vigabatrine. The response rate without relapse was higher in those treated with hormones. Long-term neurodevelopmental outcome in infants and young children with no underlying cause for their spasms was also better. Therefore, hormonal treatment was found to be superior, at least for this group of infants. This is in agreement with the findings of the UKISS trial [11]. In this blind randomized trial [11] the developmental and epilepsy outcomes of two groups of infants ($N=107$ and analysis of $n=77$) with or without identified etiology with either vigabatrine or hormonal treatment (prednisolone or tetracosactide) were compared. Seventy percent of infants treated with steroids achieved rapid spasm freedom 14 days after starting treatment compared to 54% of infants in the vigabatrine group. In all 77 infants no significant differences in outcome with respect to seizures were found at age 14 months. However, better development at follow-up at 4 years of age was found in those with unidentified etiology and allocated to the hormonal treatment group.

In a large randomized, single blinded study of 221 patients ($N=221$) [11] the effects of two different doses (high dose 100–148 mg/kg/day, ($n=107$); low dose 18–36 mg/kg/day, ($n=114$)) of vigabatrine on spasm reduction in IS were compared. More children in the high-dose group compared to the low-dose group achieved spasm freedom and achieved it quickly and with a low response rate. Remarkably the tuberous sclerosis complex (TSC) group achieved more predictable benefit by vigabatrine.

In medical practice, other AED besides vigabatrine or hormones may be tried such as valproic acid, topiramate, and diazepines. These drugs have only temporary or no effect.

Pyridoxine (B6)

Pyridoxine is easy to administer. However, experience with pyridoxine therapy outside of pyridoxine deficiency is very limited. In a randomized controlled trial, pyridoxine was provided as primary therapy, but none of the 37 infants responded [13].

In medical practice, pyridoxine is only used as an add-on therapy for a period of time in case of intractable epilepsy until a disorder of pyridoxine metabolism is excluded.

Nonpharmacologic Treatment

Ketogenic Diet

See paragraph Use of Ketogenic diet in Infants with IS.

Vagus Nerve Stimulation

Vagus nerve stimulation is not commonly used as a treatment option in IS [1].

A recent study on 55% of 69 children with intractable epilepsy showed vagus nerve stimulation was relatively safe and effective. No infants were included in this study [14].

Epileptic Surgery

A surgical approach to IS treatment depends on the detection of a focal cerebral lesion [1]. A study on infants ($N=50$) who had epileptic surgery showed that those infants with IS ($n=11$) were not differentiated in terms of outcome [15].

There is limited information regarding epileptic surgery for children with IS.

In summary, pharmacological treatment like hormones and vigabatrin are the most effective and commonly used and successful in the case of IS, especially with unidentified etiology.

In the case of TSC there is evidence that vigabatrin is the most effective and therefore should be the treatment of first choice [16].

Multiple drug regimes often lead to unacceptable side effects, especially given a relatively poor effect.

Use of Ketogenic Diet in Infants with IS

Background

The KD is not the treatment of first choice in infants with intractable epilepsy because of the assumption that the KD is nutritionally inadequate and unpalatable for the infant. Moreover, it is believed that liver function and lipid metabolism in the infant is too immature and that long-term effects are unknown. In general practice, the KD would be too difficult to handle for infants and parents.

Pilot studies by Nordli et al. [17] in 2001 and Kossoff et al. [18] in 2002 addressed whether the KD is safe, well tolerated, and effective for treating ISs. Nordli et al. [17] evaluated the outcome of 32 infants with intractable epilepsy treated with the KD. Data showed 35.5% of these children had >50% seizure reduction. An additional 19.4% of the children became seizure free. The KD appeared to be particularly effective in those children with IS; 70% (12 out of 17) had >50% improvement (of which 6 reached seizure freedom) on the KD after 3 months.

The results of Kossoff et al. were comparable to the findings of Nordli et al.

An evaluation of the efficacy, tolerability, and safety of the KD for treatment of ISs was reported in a retrospective study of 43 infants by Eun et al. [19]. They found seizure freedom in 53.5% of the infants. Adverse effects were reported in 55.8% of the infants during treatment. Some of the adverse effects were serious and a reason for discontinuation. The authors suggested revisions to the KD protocol to reduce these side effects of the KD by lowering the ketogenic ratio or nonfasting.

Kossoff et al. conducted a retrospective chart review of all infants that started the KD ($n=13$) and adeno corticotropic hormone (ACTH) ($n=20$) as a treatment option in IS [20]. The KD stopped spasms in nearly two-thirds of cases and had fewer side effects and relapses than ACTH. In the case of the latter, the EEG was normalized more rapidly. Kossoff et al. suggested a prospective study with KD as a first-line treatment option to confirm the previous findings.

Hong et al. [21] reported a large prospective single-center experiment involving 104 infants with IS treated with the KD. In this study 64% of the patients showed a >50% spasm improvement at 6 months and 77% after 1–2 years. Of these, 37% reached spasm freedom for at least a 6-month period within a median 2.4 months after starting the KD. Older age at onset of IS and fewer prior AEDs were more likely to be associated with >90% spasm improvement at 6 months. Side effects were seen in 33% of the infants. Reported side effects were constipation, weight loss, kidney stones, and gastroesohpageal reflux.

In summary, until now studies failed to demonstrate level 1 or 2 evidence that the KD is more effective in IS than other treatment options such as hormones and vigabatrine. Reported data, however, strongly suggest that the use of the KD in IS indeed is effective and the side effects are acceptable when well monitored.

In their most recent publication, Freeman and Kossoff noted the widely held misconception that the KD is dangerous in infants and young children [22].

Combination therapy with KD and other AEDs may further increase the efficacy of the KD [9].

Ketogenic Diet Initiation in Infants

Ketogenic Diet Composition

As previously mentioned, the nutritional composition of the KD differs substantially from a normal eating pattern. Examples of KD for infants are shown in Appendix 1.

At diet initiation the usual diet of the child must be gradually changed (Table 3.7) toward the KD composition.

When calculating the diet, it is important to take into account the following points:

- The recommended allowances (RDA) are recommendations for groups of healthy children, making them less suitable for individual and, possibly, handicapped children.
- Feeding problems and growth retardation are frequently seen in this particular group of children [23] and may conflict with the strict prescriptions.
- The MCT version of the KD allows a sufficient amount of protein, but this kind of diet is badly tolerated by infants. The KD formulas specially developed for infants are based on the classic version of the KD and are well tolerated by infants. When calculated carefully the RDA of protein can be supplied.
- The energy requirements of children with epilepsy may vary greatly. They depend on physical activity and may be influenced by epileptic seizures and possibly the degree of spasticity or frequency of muscle spasms during epileptic seizures [8]. It is well known that in children with neurodevelopmental disability resting energy expenditure can be deviated due to deviant body composition [23].

Table 3.7 Step by-step plan to introduce ketogenic formula [8]

Step	Regular infant formula % of volume	Ketogenic infant formula % of volume
	100	–
1	75	25
2	50	50
3	25	75
4	–	100

NB: The amount of fluid is based on RDA and infant weight and age

- A certain level of ketosis must be achieved to be certain that the metabolism has successfully changed from carbohydrate burning to fat burning. When the energy expenditure is overestimated, achieving an adequate level of ketosis will become difficult.
- The diet must be frequently adjusted to meet the changing needs of the (very) young child due to growth and developmental stage, as introduction to solid foods.
- Feeding an infant more frequently than usual (every 3–4 h) can be helpful at diet initiation to prevent side effects like vomiting, hunger, and hypoglycemia.
- The vitamin and mineral content of the diet must be calculated and supplemented on an individual basis.

Starting the Diet

The KD is usually initiated in a (neuro) pediatric hospital ward. In our experience, diet initiation at home is possible and safe under strictly monitored circumstances and thorough instructions to parents and caregivers, also in infants.

When parents are noncompliant or have limited skills, administering and monitoring the diet can be very difficult.

In the case of a medical or urgent social situation, feeding by a nasogastric tube must be considered.

Before starting the KD it is important to check if the infant has any conflicting underlying diseases and to evaluate important parameters. Inborn errors of metabolism that could lead to a severe metabolic crisis should be ruled out. These include disorders of fatty acid mitochondrial transport, β (beta)-oxidation, and other mitochondrial cytopathies [7].

Prior to starting the diet it is very important to check all AEDs, vitamin and mineral supplements, and other medications (e.g.,laxatives) for carbohydrates and make sure they are "ketoproof" (carbohydrate free). It is possible to change the medication to low-carbohydrate versions. A pharmacist can be of great help in this matter. In daily practice, 1 g (1,000 mg) of carbohydrates from AEDs and supplements is the maximum that fits into the KD regimen.

Historically, the KD was preceded by a period (24–48 h) of fasting to accelerate the ketotic state. During fasting side effects like vomiting, discomfort, and hypoglycemia frequently occurred, especially in the infant. Nowadays, the uncomfortable fasting period is increasingly omitted. Studies have shown that ketosis can also be reached without fasting beforehand without any significant impact on the effectiveness of the diet [7, 8].

To ensure that a diet with a high fat content is well tolerated by the infant, the diet will be introduced step by step. In daily practice, this means the regular formula of the infant is mixed with the KD formula (Ketocal® 3:1 or Ketocal® 4:1), as shown in Table 3.8.

Table 3.8 Recommendations for evaluation [8]

What	How	When
Ketosis		
At start	Blood or urine	Daily
When adequate	Blood or urine	Once a week, or upon indication
Seizures	Diary	Daily
	EEG	After 3 months
Growth	Weight	Once a week
	Height	Every two weeks
	Head circumference	Every two weeks
Intake		
At start	Food diary	Daily
When adequate	Food diary	Before every visit or telephone call
Side effects		
Like vomiting, constipation, etc.	Diary	Continuously
Medication		
Like AED, vitamin or mineral supplements, laxatives, etc.	Diary	Every visit

To stimulate oral motor activity and to avoid feeding aversion behavior solid foods may be introduced at age of 4-6 months. Parents will be educated on how to use a specially designed calculating program that will help them create recipes for their child that match the KD regimen. In this case, the diet will still be based on the classic KD, but adjustment to a more liberal version with a low-dose MCT is also possible.

Every infant must receive a tailor-made diet.. Not only will a daily menu be handed over to the parents, but it is also very important to give instructions on how to handle special situations like hyperketosis, food refusal, hypoglycemia, and infectious disease. Both diet and emergency regimes must be frequently adjusted for the growth, age, and developmental stage of the child.

Monitoring the Diet

During diet introduction parents often have many questions and initially often need support and confirmation that they are properly applying the diet. Frequent telephone, e-mail, or outpatient consultations with a multidisciplinary team are needed during the first weeks/months.

Evaluation

Recommendations for evaluation and medical check-ups are noted in the guidelines [7, 8] to guarantee the safety and efficacy of the diet.

Fine-Tuning

Although the diet will be carefully calculated and tailor made, it still can be a problem to reach an adequate level of ketosis.

Based on variables like the level of ketosis, it will be necessary to make adjustments to the diet, called fine-tuning the diet, to improve the outcome of the KD.

Recommendations for fine-tuning are given in Table 3.9.

Table 3.9 Recommendations for fine-tuning diet [8]

Situation	Action
Inadequate ketosis	Check calculation of recipes
	Check weight scale
	Increase ratio
	Lower kcal
Hyperketosis	Lower ratio
	Increase carbohydrates
	Increase kcal

Table 3.10 Suggestions for troubleshooting (no illness) [8]

Situation	Action
Vomiting	Give more frequently or smaller portions
	For 24 h give 50% of formula diluted with water
Food refusal	Check for constipation and reflux,
	Give more frequently or smaller portions
	Start introduction of solid foods
Out of ketosis	For 24 h give 50% of formula diluted with water
Hyperketosis >6.5 + blood >4+ urine	Give apple juice (30 mL <10 kg bodyweight, 60 mL >10 kg body weight) followed by a portion of diet formula and repeat until all values have normalized
Hypoglycemia <2.5 mmol/L	Give apple juice (30 mL <10 kg bodyweight, 60 mL >10 kg body weight) followed by a portion of diet formula and repeat until all values have normalized
Insufficient growth	Increase kcal with 5–10%
	Evaluate protein content

When fine-tuning the diet take into account that:

- In most cases, an unexpected decreased ketosis is due to incompatible medication,
- One adjustment at a time must be made in the course of a week to evaluate its effects,
- The use of carnitine to increase ketosis is still controversial.

Troubleshooting

Also in the case of food refusal, insufficient growth, or side effects, the diet must be adjusted.

Recommendations for troubleshooting are given in Table 3.10.

Special Situations

In the case of illness, the treating pediatrician should be contacted immediately because fever, diarrhea, or vomiting can alter the metabolism and level of ketosis.

Because an infant is at risk for hypoglycemia and dehydration, special attention to and close monitoring of ketosis, blood glucose, fluid intake, urine production, amount of diarrhea/vomit are very important.

In medical practice, oral dehydration salt (e.g., ORS Junior) can be used to prevent dehydration. The solution of the oral dehydration salt must be based on the carbohydrate content of the child's regular diet schedule to prevent side effects like hyperketosis (Appendix 2).

Parents should be instructed on how to act when their child becomes ill or must undergo anesthesia. Adding a tailor-made emergency regime to the child's diet plan can be very helpful in this matter [8].

In the case of illness, it is more important to treat the (acute) illness than to maintain optimal ketosis.

When a child is ill, take into account the following considerations:

- Ketone levels must be monitored more frequently in consultation with the child's pediatrician.
- Glucose levels must be monitored in the event of paleness, clamminess, or other signs that may indicate hypoglycemia.
- Fluid balance must be maintained.
- Intake of solid foods may be limited and can be accepted if the child continues to accept his or her bottle feeding.
- All vomiting or diarrhea events must be compensated with 10 mL ORS Junior/kg/body weight to prevent dehydration based on the individual diet of the child.

Evaluation of Efficacy

Three months is the most commonly used trial period to determine if the KD is having an effect on seizures [7, 8]. In the case of infants, it is recommended that the trial period be shortened to 2–4 weeks [20, 24]. Seizure frequency is evaluated by diary entries and EEG.

Positive effects on alertness, cognition, and behavior are frequently reported by parents, and, although not objective, they are important when deciding if the diet will be continued, even in the case of disappointing seizure reduction.

Tapering the Diet

The most important reason to taper the diet is insufficient effectiveness. Motivation is primarily derived from effectiveness. Our clinical experience is that the KD loses its effectiveness after a certain period. The effectiveness may last up to 3 years. It is unknown why the KD loses its effectiveness.

In the case of insufficient effectiveness, the diet can be changed back to the regular feeding pattern of the infant in 1–2 weeks' time [8].

When the KD has successfully been applied for a long period of time, the patient can revert back to his or her regular eating pattern in 2–3 months' time [7].

Medical reasons for discontinuing the diet include complications from severe, persistent adverse effects or not achieving an adequate ketosis despite fine-tuning.

In medical practice, the diet is continued as long as it is accepted by the infant and the infant's parents. In a recent article, Kang [24] compared short-term (8 months) vs. long-term (2 years) use of KD for IS to indicate how adverse effects could be minimized while efficacy and relapse rate remained strikingly similar. Tapering of the KD after 6 months in the case of seizure freedom seems justified.

Additional research is needed to corroborate this finding.

Information about follow-up with children after discontinuation of the KD is scarce. It seems that patients benefit in terms of seizure occurrence from the KD after discontinuation. One study showed that 6 years after tapering the KD seizure incidence was lower than it was prior to the start of the KD [25].

In summary, using the KD indeed implicates a rigorous, compliance-demanding therapy. It requires dedicated parents, patients, and dietitians because of the strict prescriptions. Important keys to success are tailor-made diets: taking into account as much as possible the individual possibilities and personal preferences of the infant and his or her parents [8]. Detailed emergency regimes are helpful to guarantee safety.

Conclusion

Nonpharmacologic treatment options like the KD are being increasingly used in the treatment of ISs in an effort to obtain better outcomes. With the increasing knowledge of how to apply the KD in daily practice, the availability of special ketogenic infant formulas, ketogenic calculation programs, and treatment guidelines, the KD is a safe and successful treatment option in otherwise intractable epilepsies in infants.

With the constant need of infants to grow and develop, the KD must be administered with special care and closely monitored by a multidisciplinary team.

Use of the KD may be accompanied by known and serious health consequences. In medical practice, the adverse effects are mild and can be treated in a conventional way. They are seldom cause for diet termination. Adaptations of treatment guidelines can be very helpful in the prevention and early determination of side effects of the KD.

For all these reasons the infant population is one of the most rapidly growing age groups following the KD.

Glossary

Infant Child <12 months of age.

Infantile spasms (IS): or West syndrome A form of severe epilepsy presenting between 3 and 10 months of age characterized by a brisk flexion or extension of the extremities, sometimes followed by a brief tonic posture, appearing in clusters and often occurring after sleep transition and accompanied by developmental regression. Characteristically interictal EEGs reveal hypsarrhytmia, high-amplitude, chaotic background pattern, and asynchronous slow waves intermixed with multifocal spikes.

Intractable epileptic syndrome General term covering epileptic syndromes (like Ohtarara syndrome and West syndrome) that do not respond to initial treatment with (multiple) anti epileptic drug regimes.

Ohtahara syndrome Identical to West syndrome but presenting before 3 months of age.

Ketogenic diet (KD) High-fat, low-carbohydrate diet with adequate amount of protein that mimics the metabolic state of fasting during an anabolic situation.

Due to the lack of carbohydrates energy metabolism shifts from carbohydrate to fat burning for energy, which induces production of ketone bodies (aceto acetate, β (beta)-hydroxybutyrate and acetone) that can be measured in urine and blood.

An adequate level of ketosis is defined as 3–4+(8–16 mmol/L) ketones in urine or 2–5 mmol/L ketones in blood.

Ketogenic ratio The ratio of ketone-producing foods in the diet (i.e. dietary fat). The most used ratio's are 3:1 or 4:1. This means either 3 or 4 g of ketone-producing fat vs. 1 g non-ketone-producing protein and carbohydrates.

Appendix 1: Diet Schedules for Infants

Example I: 9 Months Old (9 kg)

Bottle feeding/day

Ingredients/24 h

- 70 g Ketocal 3:1®
- 12 mL Calogen® neutral
- Water until 800 mL of feeding

Supplement

- 5 μg vitamin D solute into oil

Divided into

- 3 × 200 mL
- 2 × 100 mL

Breakfast	200 mL bottle feeding
Morning snack	Fruit at 2.5 g carbohydrate[a]
	25 g crème fraiche (35 g/100 gram fat)
	100 mL bottle feeding
Afternoon	200 mL bottle feeding
Afternoon snack	Vegetables at 1 g carbohydrate[a]
	5 g vegetable oil
	5 g fatty cheese (48 g fat/100 g)
	100 mL bottle feeding
Evening meal	200 mL bottle feeding

[a]According to variation lists

Analysis		
Calories per day	705	78 kcal/kg
Grams of protein	13	7 energy %
Grams of LCT fat	69	88 energy %
Grams of carbohydrates	9	5 energy %
Ratio	3:1	

Example II: 9 Months Old (8.5 kg) with Decreased Resting Energy Expenditure

Bottle feeding/day

Ingredients/24 h

- 85 g Ketocal® 3:1
- 710 mL water

Supplement

- 5 mg vitamin D solute in oil

Divided into

- 5 × 150 mL

Extra

- 1 × 100 mL water/sugar-free lemonade

Breakfast	150 mL bottle feeding
Morning	150 mL bottle feeding
	100 mL sugar-free lemonade
Afternoon	150 mL bottle feeding
Afternoon snack	Vegetables/cream/oil/ cheese calculated based on analysis of 150 mL bottle feeding[a]
	100 mL sugar-free lemonade
	NB: when the child eats only 50% of his or her meal, supplement 75 mL Bottle feeding
Evening	150 mL bottle feeding

[a]Analysis of 150 mL bottle feeding made of 17 g Ketocal® 3:1:
119 kcal, 2.6 g protein, 12 g LCT fat, 1 g carbohydrate, ratio 3:1

Analysis		
Calories per day	594	69 kcal/kg
Grams of protein	13	8 energy %
Grams of LCT fat	58	88 energy %
Grams of carbohydrates	6	4 energy %
Ratio	3:1	

Appendix 2: Emergency Regimes in Case of Illness [8]

Use of ORS Junior

100 mL ORS Junior, prepared according to the information on the package, contains 22 g carbohydrate (2 sachets for 1 L)

1. 1 sachet ORS Junior can be diluted into 1,000 mL water and contains 11 g carbohydrate.
2. The amount of ORS Junior depends on the carbohydrate content of the KD and must be calculated individually.
3. In daily practice, in the case of the classic KD, a limited amount of ORS Junior can be used.

Illness, fever *with* vomiting or diarrhea	
Phase I	Give 24 h ORS Junior according to the preceding guidelines and calculated based on weight and age of individual child
	Compensate each time vomiting and or diarrhea occurs with 10 mL ORS Junior/kg body weight
	Use diet composition indicated in individual emergency plan
Phase II	In case of bottle feeding
	Dilute bottle feeding 50–50 with water
	Give numerous, smaller portions throughout day
	In case of solid food
	Calculate meals at a lower ratio than the usual diet (2.5:1 when normal 3:1, or 3:1 when normal 4:1)
	Distribute the food over smaller portions
	Compensate each vomiting/diarrhea episode with 10 mL ORS Junior/kg body weight
	Use composition indicated in individual emergency plan
	Intake of solid foods may be limited and can be accepted if child continues to feed from bottle
Phase III	If complaints subside, a switch can be made to the regular diet
Illness, fever *without* vomiting and/or diarrhea	
Phase I	In case of bottle feeding
	Dilute bottle feeding 50–50 with water
	Give numerous, smaller portions throughout day
	In case of solid food
	Calculate meals at a lower ratio than the usual diet (2.5:1 when normal 3:1, or 3:1 when normal 4:1)
	Distribute food over smaller portions
	Compensate each vomiting/diarrhea episode with 10 mL ORS Junior/kg body weight
	Use composition indicated in individual emergency plan
	Intake of solid foods may be limited and can be accepted if child continues to feed from bottle
Phase II	If complaints subside, a switch can be made to the regular diet
	If complaints do not subside, see advice under Phase I
	First 24 h can be continued for a maximum of 2 days

References

1. Wheless JW. Nonpharmacologic treatment of the catastrophic epilepsies of childhood. Epilepsia. 2004;45 Suppl 5:17–22.
2. Wheless JW. History of ketogenic diet. In: Stafstrom CE, Rho JM, editors. Epilepsy and the ketogenic diet. 1st ed. Totowa, NJ: Humana; 2004. p. 349.
3. Freeman JM, Freeman JB, Kelly MT. The ketogenic diet: a treatment option for epilepsy. 3rd ed. New York: Demos Medical Publishing; 2000.
4. Levy R, Cooper P. Ketogenic diet for epilepsy. Cochrane Database Syst Rev. 2003;(3):CD001903.
5. Levy RG, Cooper PN, Giri P. Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database Syst Rev. 2012;3:CD001903.
6. Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol. 2008;7(6):500–6.
7. Kossoff EH, Zupec-Kania BA, Amark PE, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. Epilepsia. 2009;50(2):304–17.
8. van den Hurk T, van der Louw E. Dietary treatment guideline for the ketogenic diet in children with refractory epilepsy. Evidence based manual for multidisciplinairy treatment. 1st ed. Utrecht: University Medical Center Utrecht, Department of Nutritional Sciences and Dietetics; 2011.
9. Kossoff EH. Infantile spasms. Neurologist. 2010;16(2):69–75.
10. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. Cochrane Database Syst Rev. 2008(4):CD001770.
11. Darke K, Edwards SW, Hancock E, et al. Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: a multi-centre randomised trial. Arch Dis Child. 2010;95(5):382–6.
12. Elterman RD, Shields WD, Bittman RM, Torri SA, Sagar SM, Collins SD. Vigabatrin for the treatment of infantile spasms: final report of a randomized trial. J Child Neurol. 2010;25(11):1340–7.
13. Debus OM, Kurlemann G. Sulthiame in the primary therapy of West syndrome: a randomized double-blind placebo-controlled add-on trial on baseline pyridoxine medication. Epilepsia. 2004;45(2):103–8.
14. Kabir SM, Rajaraman C, Rittey C, Zaki HS, Kemeny AA, McMullan J. Vagus nerve stimulation in children with intractable epilepsy: indications, complications and outcome. Childs Nerv Syst. 2009;25(9):1097–100.
15. Loddenkemper T, Holland KD, Stanford LD, Kotagal P, Bingaman W, Wyllie E. Developmental outcome after epilepsy surgery in infancy. Pediatrics. 2007;119(5):930–5.
16. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. Epilepsia. 2010;51(10):2175–89.
17. Nordli Jr DR, Kuroda MM, Carroll J, et al. Experience with the ketogenic diet in infants. Pediatrics. 2001;108(1):129–33.
18. Kossoff EH, Pyzik PL, McGrogan JR, Vining EP, Freeman JM. Efficacy of the ketogenic diet for infantile spasms. Pediatrics. 2002;109(5):780–3.
19. Eun SH, Kang HC, Kim DW, Kim HD. Ketogenic diet for treatment of infantile spasms. Brain Dev. 2006;28(9):566–71.
20. Kossoff EH, Hedderick EF, Turner Z, Freeman JM. A case–control evaluation of the ketogenic diet versus ACTH for new-onset infantile spasms. Epilepsia. 2008;49(9):1504–9.
21. Hong AM, Turner Z, Hamdy RF, Kossoff EH. Infantile spasms treated with the ketogenic diet: prospective single-center experience in 104 consecutive infants. Epilepsia. 2010;51(8):1403–7.
22. Freeman JM, Kossoff EH. Ketosis and the ketogenic diet, 2010: advances in treating epilepsy and other disorders. Adv Pediatr. 2010;57(1):315–29.
23. Sullivan PB. Feeding and Nutrition in children with neurodevelopmental disability. 1st ed. London: Mac Keith; 2009.
24. Kang HC, Lee YJ, Lee JS, et al. Comparison of short- versus long-term ketogenic diet for intractable infantile spasms. Epilepsia. 2011;52(4):781–7.
25. Patel A, Pyzik PL, Turner Z, Rubenstein JE, Kossoff EH. Long-term outcomes of children treated with the ketogenic diet in the past. Epilepsia. 2010;51(7):1277–82.
26. Wheless JW. Managing severe epilepsy syndromes of early childhood. J Child Neurol. 2009;24(8 Suppl):24S–32. quiz 33S-26S.
27. Conry JA. Pharmacologic treatment of the catastrophic epilepsies. Epilepsia. 2004;45 Suppl 5:12–6.
28. Jonas R, Asarnow RF, LoPresti C, et al. Surgery for symptomatic infant-onset epileptic encephalopathy with and without infantile spasms. Neurology. 2005;64(4):746–50.

Chapter 4
Short Bowel Syndrome: Management and Treatment

Joanne F. Olieman, Hanneke I. Jsselstijn, Barbara A. de Koning, and Dick Tibboel

Key Points

- There is no consensus on the definition of short bowel syndrome.
- Management and treatment of short bowel syndrome is complex.
- Breast milk is the preferred type of nutrition.
- Interdisciplinary approach is required for optimal outcome.

Keywords Short bowel syndrome • Enteral and parenteral nutrition • Bowel adaptation growth and interdisciplinary management

Introduction

Intestinal failure is defined as the critical reduction of functional gut mass below the amount that is minimally necessary for adequate digestion and absorption to satisfy nutrient and fluid requirements for growth in children [1]. Therefore the use of parenteral nutrition (PN) is required. Intestinal failure may result from intestinal obstruction, dysmotility, surgical resection, congenital defects, or disease-associated loss of absorption [2]. Intestinal failure may be caused by short bowel syndrome (SBS), mucosal enteropathy, or dysmotility syndromes [3]. SBS is a subcategory of intestinal failure, which may result from surgical resection, congenital defect, or disease-associated loss of absorption. This condition is characterized by the inability to maintain protein–energy, fluid, electrolyte, or micronutrient

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balances when on a conventionally accepted, normal diet [2]. Numerous definitions of SBS have been proposed, such as the American definition by O'Keefe et al. [2], but regrettably there is no worldwide consensus on a generally applicable clinical definition [3, 4]. Essentially, authors disagree on whether the diagnosis should solely refer to either remaining bowel length or to duration of postoperative PN, or to a combination of both. Establishing the remaining bowel length is hampered by practical problems, and thus it seems tentative to base the definition of SBS on its clinical presentation solely, rather than on anatomical aspects.

In early childhood, SBS may result from massive resection of the small intestine necessitated by volvulus, congenital malformations such as intestinal atresia and gastroschisis, or necrotizing enterocolitis (NEC) [1, 5–7]. Some of the underlying diseases, such as gastroschisis and intestinal atresia, not only affect residual bowel length, but also may influence its residual function and adaptation potential [8]. Successful bowel adaptation refers to the capacity of structural and physiological alterations of the bowel that allow children with SBS to grow healthily while receiving oral and/or enteral nutrition. There is a range of factors that may predict whether adaptation will be successful. These include: age, underlying diagnosis leading to SBS, length and section of small and/or large bowel resected, presence or absence of the ileocecal valve and/or colon, intrinsic adaptive potential of remaining bowel, health of other organs involved in digestion and absorption, and the presence or absence of bacterial overgrowth of the small intestine [9]. Furthermore, the long-term outcome is determined by the rate at which enteral feedings can be provided postoperatively while the child is on parenteral nutrition (PN), and by the type of enteral feedings [9].

Infantile SBS has significant morbidity and is potentially lethal—especially when intestinal loss is extensive [10]. A multitude of complications may occur secondary to long-term hospitalization and prolonged PN, such as central line-related complications, multiple systemic infections, PN-associated liver disease (PNALD), and failure to thrive [11]. Major predictors of mortality in pediatric SBS are PN-associated cholestasis and shorter age-adjusted remaining small bowel length [12]. On the other hand, intestinal continuity and preservation of the colon are predictors of survival [11, 13]. PNALD is one of the most common and severe morbidities in children with infantile SBS. It is associated with a mortality rate approaching 100% within 1 year of diagnosis when children cannot be weaned off PN or will not receive a liver/small bowel transplant [11]. One study demonstrated a 25% prevalence of PNALD in 36 patients with chronic intestinal failure, of whom 43% had SBS [14]. A review estimated that generally 30–60% of children develop hepatic dysfunction while receiving long-term PN [15]. Risk factors for developing PNALD include prolonged PN, prematurity, frequent surgical procedures, lack of enteral intake and thus disruption of the enterohepatic cycle, intestinal stasis with subsequent bacterial overgrowth, early and/or recurrent catheter-related sepsis [9, 16, 17].

Survival rates of neonatal SBS patients have considerably improved over the years, reaching 70–90% [11, 13, 18–20]. This progress is mainly due to improved composition of PN, improved protocols for handling central venous catheters (CVC), interdisciplinary patient management and better outcomes of small bowel transplantation. Still, reported mortality rates vary from 6 to 47% [11, 13, 18–24] and have not declined over the years. This discrepancy might be explained by different definitions of SBS used, differences in measured/documented bowel lengths, and differences in durations of PN dependency.

Maintaining simultaneously optimal nutritional status and achieving intestinal adaptation is a clinical challenge in patients with SBS. Both growth and development of the child as well as bowel adaptation should be considered synergistically as primary outcome parameters. The aim of this chapter is discussing several issues for the nutritional management including parenteral nutrition, bowel adaptation, and the type of diet to be used and the route of its delivery: orally and/or enterally.

Nutrition and Short Bowel Syndrome

The clinical manifestation of SBS is determined by the residual length of the jejunum and ileum, the presence of an enterostomy, the presence (or absence) of the ileocecal valve, the remaining functional length of the colon, underlying pathology and possible complications [13]. These factors affect bowel adaptation and therefore the functionality of the gastrointestinal tract, which in turn affects feeding options. Therefore, recommendations for the type and duration of parenteral and enteral nutrition are variable, with the child's age as an additional key factor. The goals of nutritional support in patients with SBS are twofold: (1) providing safe, adequate supplemental nutrients to preserve lean body mass and function, and (2) if possible, supporting and accelerating the body's own adaptive mechanisms [25]. Therefore, different approaches are needed, especially in the first acute phase of SBS. For example, when aiming at providing as many calories as possible, one might choose a type of enteral nutrition that differs from that aiming at promoting bowel adaptation.

Parenteral Nutrition

After resection, PN is inevitable in order to meet the energy requirements. Some patients will require supplemental PN for a limited period only—that is—when intestinal adaptation is successful. Others will remain dependent on parenteral support (irreversible intestinal failure) and may be considered candidates for bowel transplantation when life-threatening complications develop [9, 16, 26], such as PNALD. Generally, 30–60% of children will develop hepatic dysfunction while receiving long-term PN [15]. The 1-year survival rate after intestinal transplantation has reached 80% [27]; the average survival rate 5 years after transplantation is 50% [28], compared to >80% in non-transplanted patients without hepatobiliary complications of PN [29]. Patients on PN are at risk for fatty liver, hepatic fibrosis, and cholestasis [30]. The exact mechanisms are unknown, but multifactorial etiology has been proposed implicating host factors such as a reduced bile acid pool or toxic constituents of the PN solution such as excessive protein and excessive glucose infusion rates [31]. The observation that reduced quantities of parenteral soy-based lipid delays the onset of cholestasis has led to the development of liver sparing PN protocols. If parenteral soy-based lipid is limited to <0.5 g/kg/day, cholestasis may be reduced or even prevented [32]. Reduction in lipid calories must be compensated by a concomitant increase in glucose calories which can result in an excessive glucose infusion rate, hyperinsulinemia, hypertriglyceridemia, and increased septic risk [33]. Recently a few studies have shown that parenteral fish oil emulsion reverses PNALD [34–36]. New lipid emulsions, based on the mixture of four different oils including fish oil, might be the most balanced source of lipids for SBS patients at risk of developing cholestasis [37].However randomized controlled trials on these novel lipid emulsions are lacking.

Cyclical PN may commonly be provided as soon as metabolic status allows it. Its aim is to reduce the permanent hyperinsulinaemia with subsequent fat accumulation and liver disease [38–40]. Cyclical PN allows a more important mobilization of the energetic stocks and physical activity during the day than continuous PN and might change the quality of the weight gain and avoid an unnecessary storage of lipid deposits [38]. In general, cyclical PN allows increasing enteral and oral nutrition throughout the day. Glucose tolerance should be monitored. A stepwise increase and decrease of glucose infusion rates at onset and at discontinuation of the PN infusion respectively should be considered to avoid strong fluctuations in blood glucose levels. The stepwise change in glucose infusion rate is called tapering and should be considered when 75% of the caloric intake is provided by PN and cyclic administration is desired. Moreover cyclical PN allows for more physical activity and is therefore practical for PN in the home situation.

Nutrition and Bowel Adaptation

Shortly after bowel resection the remaining part of the bowel attempts to increase its fluid and nutrient absorption [26]. This process includes muscular hypertrophy and mucosal hyperplasia [41]. It is generally accepted that enteral nutrition enhances bowel adaptation. The mechanism by which enteral nutrients stimulate adaptation is complex and three major mechanisms have been described: stimulation of: (1) mucosal hyperplasia by direct contact with epithelial cells; (2) trophic gastrointestinal hormone secretion; and (3) the production of trophic pancreatobiliary secretions [26, 42]. Luminal factors include a variety of nutrients, secretions, and other essential components in the diet or produced in the lumen of the gastrointestinal tract that have been known to stimulate gut mucosal growth [43]. Suggested luminal factors are presented in Textbox 30.1 [26, 42, 44]. After neonatal small intestinal resection it may take up to 5 years or longer before adaptation is complete. The composition of the diet should be considered in an effort to balance gastrointestinal tolerance with specific nutrients in a complex form that may further stimulate the adaptive process [44].

Textbox 30.1: Luminal Factors in Bowel Adaptation

- *Nutrients*
  - Long chain triglycerides (LCT)
  - Proteins
  - Glutamine
  - Dietary fiber
- *Hormones*
  - Enteroglucagon
  - Growth hormone
  - Glucagon-like peptide 2
  - Cholecystokinin
  - Gastrin
  - Neurotensin
  - Glucagon-like peptide YY
- *Growth factors*
  - Epidermal growth factor (EGF)
  - Insulin-like growth factor I (IGF-I)
- *Prostaglandines*
- *Polyamines*

Glutamine

A potential candidate as supplement to enhance bowel adaptation is glutamine. Glutamine is known to serve as a metabolic substrate for the small intestine. Four major findings support its candidacy: (1) Glutamine is an essential fuel for the enterocyte and for immune cells and cannot be substituted by other amino acids; (2) during periods of stress, a state of relative glutamine deficiency exists, as evidenced in plasma glutamine levels; (3) supplementation of exogenous glutamine delivers essential fuel to tissues in need; (4) the small intestinal mucosa becomes atrophic when the gut is deprived of glutamine, as in the case during total parenteral feeding [45]. Parenteral glutamine supplementation

in animals following massive intestinal resection enhanced mucosal hyperplasia [46, 47]. One study found that increasing glutamine content of feeds to 25% of total amino acids produced, enhanced jejunal and ileal hyperplasia, even on a hypocaloric feed, and improved overall weight gain [48]. On the other hand several other animal studies could not demonstrate a stimulatory effect of glutamine-enriched enteral nutrition on adaptation [49–51]. At present, studies in humans are very limited. Glutamine supplementation of parenteral nutrition in newborns and infants after major digestive surgery did not decrease sepsis rate [52]. Neither did enteral glutamine supplementation affect the sepsis rate in 314 very low birth weight (VLBW) infants [53]. Others showed that enteral glutamine supplementation in VLBW infants decreased the sepsis rate but did not improve feeding tolerance [54]. In six studies in adults with SBS, glutamine was administered orally and/or intravenously for 28–56 days, which did not result in significant changes in the surrogate parameters tested in four studies [55–58]. The two other studies showed a significant increase in lean body mass [59, 60]. In conclusion, even though the animal studies were encouraging, so far neither enteral nor parenteral supplementation of glutamine has proven to enhance bowel adaptation.

Dietary Fiber

Another luminal nutrient potentially enhancing bowel adaptation is dietary fiber. Fiber can be subdivided into soluble and insoluble forms. Insoluble forms (e.g., cellulose found in cereals) bind to water and cause bulking and softening of the stool and decrease whole gut transit time. Soluble fiber (e.g., pectin, guar gum found in fruits and vegetables) slow gastric emptying and overall gut transit time, resulting in a mild antidiarrheal effect [61, 62]. Bacterial fermentation of soluble fiber in the colon produces short chain fatty acids (SCFAs), which are an important source of energy [63]: SCFAs account for 5–10% of the total energy requirements [64]. Animal studies have shown that pectin enhanced bowel adaptation [65, 66]. There are no human studies on the effect of pectin on bowel adaptation. Only one case study reported that pectin supplementation in a single patient caused a prolonged transit time and higher nitrogen absorption [67].

Breast Milk

The health benefits of breast milk have been amply documented; its use is associated with significantly decreased risks of infection, allergy, respiratory diseases, diabetes, and otitis media [68]. Exclusively breastfed children have reduced risk of infectious diseases such as diarrhea and respiratory infections [69]. It has been postulated that breast milk, which contains glutamine and growth factors (e.g., growth hormone and epidermal growth factor), might also enhance bowel adaptation [5, 26]. A few cohort studies have demonstrated that breast milk contains high amounts of nucleotides, immunoglobulin A, and leucocytes, which support the immune system of the neonate [70, 71]. One study found that breastfed infants with SBS were weaned off PN earlier than non-breastfed SBS infants [72]. Human studies on the effect of breast milk on bowel adaptation are lacking. However, some studies have suggested that breast milk decreases the risk of NEC in newborns [73–76]. One third of all NEC patients require surgical intervention, and a quarter of those patients develop SBS [77]. Approximately 30% of all SBS patients had NEC as the underlying diagnosis [78]. Therefore it might even be hypothesized that breast milk might prevent NEC to some extent and thus lowers the incidence of SBS.

Donor breast milk is an alternative form of milk when the mother's own milk is not available or is in short supply [76]. The use of donor breast milk varies across the world [76]. Donor milk is pasteurized (heated to 62.5°C for 30 min) and then frozen. This process inactivates HIV, cytomegalovirus,

and other viruses, but also affects the nutritional and immunological properties of breast milk [79]. These properties of breast milk might be important for bowel adaptation. Although a few studies have shown that donor breast milk also decreases the risk of developing NEC compared to formula feeding [75, 76], it is unknown whether donor breast milk also has the potential to enhance bowel adaptation.

Strong evidence continues to demonstrate that breast milk is the optimal source of nutrition for infants. It is associated with lower rates of infection diseases during infancy and therefore also recommended as the first choice of enteral feeding in SBS patients [4].

Randomized controlled trials are needed to investigate the role of (donor) breast milk on bowel adaptation. Other randomized controlled trials should confirm the advantages of (donor) breast milk over formula feeding, with enteral tolerance and time to enteral autonomy as primary endpoints.

Enteral Nutrition

The route of administration and composition of the diet of children with SBS are best determined on the basis of the underlying disease, location and length of the remaining bowel, presence of the colon, and the child's age. After the acute phase children with SBS have normal energy requirements. However, due to poor bowel function shortly after resection, they inevitably need PN at first. Gradually, as the remaining bowel adapts, the amount of enterally administered nutrients can be increased. Based on clinical experience, PN will often be needed for a considerable period of time along with enteral nutrition in order to maintain normal growth [4]. The optimal enteral feeding regimen in children with SBS is still debated by clinicians. Subjects of debate are mode of administration (continuous versus bolus feedings), time of introduction in general, composition (polymeric, semi-elemental, or elemental), time of introduction and composition of oral feeding, and the supplementation of fibers. Most data on enteral nutrition in children with SBS are derived from outcomes of retrospective observational studies and/or case reports [5]; relevant high-quality randomized controlled (clinical) trials are scarce. In a recent review of the literature the current state of the research in children with SBS was presented and evidence-based recommendations where possible (according to the Scottish Intercollegiate Guidelines Network criteria (SIGN) [80]) were given [4]. In the absence of evidence, clinical recommendations were based on expert opinion.

Evidence-Based Recommendations

Enteral nutrition should be initiated as soon as possible (i.e., a few days after bowel resection) to promote intestinal adaptation. This supposition is supported in the literature by level 1 studies [81, 82]. Breast milk or standard polymeric formula (depending on age) is the recommended initial feed (level 1 and 3 studies) [72, 83].

Recommendations Based on Clinical Experience

Based on clinical experience, it is recommended to gradually increase the volume of enteral nutrition by twice-weekly adjustments [84]. When higher amounts of enteral nutrition are well tolerated (i.e., no vomiting, no increased volume of diarrhea), the amount of PN can be reduced accordingly, because

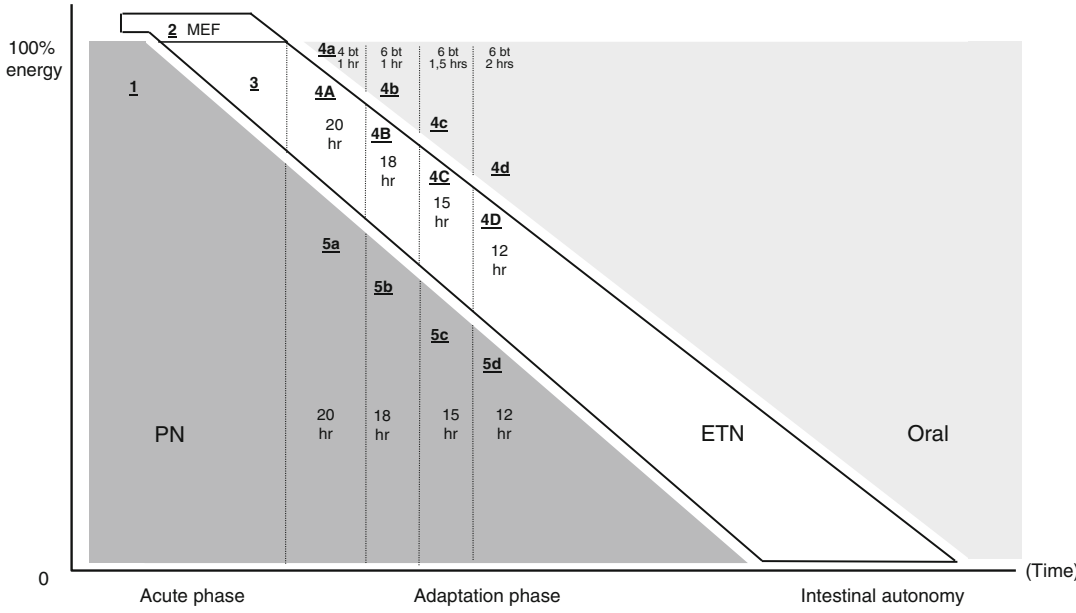

Fig. 4.1 Proposed systematic nutritional strategy. The numbers in the figure correspond with the steps presented in Table 4.1. *PN* parenteral nutrition, *MEF* minimal enteral feeding, *ETN* enteral tube nutrition, *bt* bottle, *hr* hour

not all enterally administered calories are absorbed, PN should not be decreased isocalorically. In addition, it is recommended to administer enteral nutrition in a continuous fashion [41, 85]. When half of the energy requirements are provided by enteral nutrition in a continuous fashion (the other half by PN), the feeding mode may be changed to intermittent administration of enteral nutrition [41]. Gastric feeding is the most physiological method of administration, but in case of vomiting and/or gastric retention, enteral nutrition can be administered past the pylorus via a duodenal or jejunal tube. In order to stimulate the neonate's suck and swallow reflexes, small volumes of bottle feeding should be started as soon as possible [41, 84]. Solid foods may be introduced at the age of 4–6 months (if necessary corrected for gestational age) to stimulate oral motor activity and to avoid feeding aversion behavior [5, 41, 84, 86]. When the colon is present, soluble fibers can be added to the diet [67, 87].

Multicenter prospective studies on the effects of feeding strategies on bowel adaptation, fecal production, linear growth, and clinical outcome are required to find the optimal feeding regimen in children with SBS.

Previously clinical management was based on "trial and error". At the time of writing, it is not possible to solely base the desired nutritional regimen of children with SBS on evidence obtained from previous scientific studies [4]. Multiple studies have shown that there is still room for improvement of care in this vulnerable group of patients. It is important to provide continuity of care, especially in dietary management. Even though the manifestation of SBS is variable in every patient and care should be tailor-made, it is important to have systematic nutritional strategies that can be adapted to the patient's specific needs. In Fig. 4.1 and the accompanying Table 4.1 a systematic nutritional strategy is proposed based on the findings of our research, current literature, and our own clinical experience. It consists of a visual time frame based on the phases of SBS [41]. It is not possible to present exact time intervals in days/months/years, because the course of the disease varies in every patient. Minimal enteral feeding is placed on top of the 100% energy intake, because it is not considered to provide energy, but rather as luminal nutrient for bowel adaptation. Oral feeding can be used

Table 4.1 Proposed systematic nutritional strategy infantile SBS

Step	Description	Start	Components	Type	Starting dose	Dose increase/decrease	Conditions
1	Full PN	Directly post-op	PN	Glucose, amino acids, and lipids	Full RDA		
2	Introduction MEF	1–2 days post-op	PN	Glucose, amino acids, and lipids	Full RDA		
			MEF	Breast milk or polymeric	24 × 1 ml/h continuously	2× a week increase with 1 ml/h, until ED is reached	No vomiting, extensive diarrhea
3	Introduction ETN	When ≥ ED ml/h	TPN	Glucose, amino acids, and lipids		Decrease isovolemic, with attention to calories	When increasing ETN and oral
			ETN	Breast milk or polymeric[a]	24× ≥1 ml/kg/h continuously (=24 × ≥ ED ml/h)	2× a week increase with 1 ml/h	No vomiting, extensive diarrhea
4	Introduction oral feed	As soon as possible	PN	Glucose, amino acids, and lipids		Decrease isovolemic, with attention to calories	When increasing ETN and oral
			ETN	Breast milk or polymeric[a]	(a) 20× D ml/h (b) 18× D ml/h (c) 15× D ml/h (d)12× D ml/h	2× a week increase with 1 ml/h	Do not increase volume and frequency bottle at same time, no extensive vomiting/diarrhea
			Oral	Breast milk or polymeric[a]	(a) 4 bottles 1 hour dose (b) 6 bottles 1 hour dose (c) 6 bottles 1.5 h dose (d) 6 bottles 2 h dose	2× a week increase with 1 ml/h	ETN stop on time bottle, no extensive vomiting/ diarrhea
5	Cycling TPN	(a) 25% cal ETN and oral (b) 30% cal ETN and oral (c) 40% cal ETN and oral (d) 50% cal ETN and oral	PN	Glucose, amino acids, and lipids	(a) 20 h/day (b) 18 h/day (c) 15 h/day (d) 12 h/day		No hypoglycemia

PN parenteral nutrition, *ETN* enteral tube nutrition, *MEF* minimal enteral feeding (≤24 ml/kg/day), *ED* enteral dose (≥24 ml/kg/day), *D* dose

[a]Type of nutrition depends on age and/or availability of breast milk

at the same time as continuous enteral feeding therapy. We recommend introducing bottle feeding as soon as possible to stimulate the suck and swallow reflex. For example, stop continuous enteral feeding for 1 h and give 1 h dose per bottle (*step 4*, Table 4.1).

It is important to increase the volume of enteral feeding not too aggressively, as an aggressive strategy will probably cause osmotic diarrhoea and/or vomiting. Therefore we advocate patience and a strategy in which the volume is slowly increased by 1 ml/h twice a week. In addition, we recommend the use of breast milk as the preferred type of enteral feeding. Moreover, it should be considered to set up a donor milk bank to provide donor breast milk when the mother's breast milk is not available.

Interdisciplinary Management

Several institutions have developed intestinal rehabilitation programs in response to increasing concerns about morbidity following infantile bowel resection [88–93]. The ultimate goal of these programs is to optimize intestinal adaptation while preserving adequate growth and development. A few studies have shown that an interdisciplinary SBS program, coordinating both inpatient and outpatient management, improved patients' clinical outcome [88, 91, 92]. A rehabilitation program may have a surgical component, i.e., lengthening the remaining small bowel in order to increase nutrient and fluid absorption, by either slowing the transit time or increasing the surface area [16]. Intestinal lengthening procedures take advantage of the bowel dilatation that often occurs in the foreshortened remaining small bowel [9]. One of these lengthening procedures is called serial transverse enteroplasty procedure (STEP) [94]. A recent study reported that after a median follow-up of 12.6 months after STEP, enteral tolerance increased by 116% in 38 patients and that nearly half of them had been weaned off PN [94].

As stated earlier, PNALD is one of the most common morbidities. Early enteral feeding may slow its progression and may even reverse it once PN is discontinued and full enteral autonomy is reached [95]. Discontinuing PN is challenging in SBS patients who have not yet reached complete bowel adaptation and therefore still have poor bowel function [96].

As reported above, SBS is a surgical and medical disorder associated with potentially life-threatening complications and long-lasting dependence on artificial nutrition. In earlier days, the management of patients with SBS was typically in the hands of several individuals, all specialists in their own discipline. Yet, to effectively meet the complex medical, psychological, and social needs of these patients and to guarantee continuity of care, it is increasingly acknowledged that treatment of SBS is best accomplished by an interdisciplinary team [9]. Such a team should include pediatric gastroenterologists and surgeons, specialized nurses, dieticians, social workers, and psychologists [89]. Interdisciplinary teams are likely to be of particular value in early identification of patients at risk for long-term PN dependency, the first step toward avoiding severe complications. Close monitoring of nutritional status, steady and early introduction of enteral nutrition, and aggressive prevention, diagnosis, and treatment of infections such as catheter-related sepsis and bacterial overgrowth can significantly improve the prognosis [9].

One study described nutritional outcomes and resource consumption of ten children with infantile SBS followed by the interdisciplinary SBS team [97]. Management of these children makes a substantial claim on health care resources, with an average total cost of €269,700 per patient. The costs were mainly comprised of hospital admissions (82%), with many of the readmissions being caused by (central catheter-related) sepsis. This study concluded that Home PN and interdisciplinary management reduces the risk of sepsis [97].

As the costs mainly comprise hospital admissions, early HPN could contribute to cost reduction. Systematic nutritional strategies are essential to wean SBS patients off PN as soon as possible and thus prevent, delay, or reverse complications such as PNALD. Interdisciplinary teams have the potential to facilitate early HPN and to optimize growth by tailor-made treatment. The interdisciplinary

team should be involved in the treatment immediately after the initial surgical intervention so that continuity of care can be guaranteed. Moreover the team can educate parents in HPN as soon as possible, which enables early discharge of these patients with concomitant reduction in costs and improvement of quality of life for patients and their families. Improved care has led to increased survival rates of infants with SBS, but little information is available on the long-term impact of infantile SBS on growth and physical development. One study showed that patients 5–30 years after infantile SBS had shorter stature, low bone mineral content, but normal weight for height and percentages of body fat [98]. This might be explained by the low energy intake and intestinal bowel dysfunction reported [98]. These results show that continuing follow-up into adulthood is important even after subjects have reached nutritional autonomy.

Conclusion

The management of SBS is complex and should be in care of the interdisciplinary team. Cyclical PN may commonly be provided as soon as metabolic status allows it. The type of parenteral fat should be considered in order to avoid or treat PNALD. Enteral feeding should be started as soon as possible and breast milk is the preferred type of nutrition. It is recommended that enteral nutrition should be administrated in a continuous fashion. Multicenter prospective studies on the effects of feeding strategies on bowel adaptation, fecal production, linear growth, and clinical outcome are required to find the optimal feeding regimen in children with SBS.

References

1. Goulet O, Ruemmele F. Causes and management of intestinal failure in children. Gastroenterology. 2006;130 (2 Suppl 1):S16–28.
2. O'Keefe SJ, Buchman AL, Fishbein TM, Jeejeebhoy KN, Jeppesen PB, Shaffer J. Short bowel syndrome and intestinal failure: consensus definitions and overview. Clin Gastroenterol Hepatol. 2006;4(1):6–10.
3. Wales PW, Christison-Lagay ER. Short bowel syndrome: epidemiology and etiology. Semin Pediatr Surg. 2010;19(1):3–9.
4. Olieman JF, Penning C, Ijsselstijn H, et al. Enteral nutrition in children with short-bowel syndrome: current evidence and recommendations for the clinician. J Am Diet Assoc. 2010;110(3):420–6.
5. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology. 2003;124(4):1111–34.
6. Jeejeebhoy KN. Management of short bowel syndrome: avoidance of total parenteral nutrition. Gastroenterology. 2006;130(2 Suppl 1):S60–S6.
7. Koffeman GI, van Gemert WG, George EK, Veenendaal RA. Classification, epidemiology and aetiology. Best Pract Res Clin Gastroenterol. 2003;17(6):879–93.
8. Bruzoni M, Sudan DL, Cusick RA, Thompson JS. Comparison of short bowel syndrome acquired early in life and during adolescence. Transplantation. 2008;86(1):63–6.
9. Duro D, Kamin D, Duggan C. Overview of pediatric short bowel syndrome. J Pediatr Gastroenterol Nutr. 2008;47 Suppl 1:S33–S6.
10. Booth IW, Lander AD. Short bowel syndrome. Baillieres Clin Gastroenterol. 1998;12(4):739–73.
11. Wales PW, de Silva N, Kim JH, Lecce L, Sandhu A, Moore AM. Neonatal short bowel syndrome: a cohort study. J Pediatr Surg. 2005;40(5):755–62.
12. Spencer AU, Neaga A, West B, et al. Pediatric short bowel syndrome: redefining predictors of success. Ann Surg. 2005;242(3):403–9. discussion 409–412.
13. Quiros-Tejeira RE, Ament ME, Reyen L, et al. Long-term parenteral nutritional support and intestinal adaptation in children with short bowel syndrome: a 25-year experience. J Pediatr. 2004;145(2):157–63.
14. Diamanti A, Gambarara M, Knafelz D, et al. Prevalence of liver complications in pediatric patients on home parenteral nutrition: indications for intestinal or combined liver-intestinal transplantation. Transplant Proc. 2003;35(8):3047–9.

15. Buchman A. Total parenteral nutrition-associated liver disease. JPEN J Parenter Enteral Nutr. 2002;26 (5 Suppl):S43–S8.
16. Goulet O, Sauvat F. Short bowel syndrome and intestinal transplantation in children. Curr Opin Clin Nutr Metab Care. 2006;9(3):304–13.
17. Beath SV, Davies P, Papadopoulou A, et al. Parenteral nutrition-related cholestasis in postsurgical neonates: multivariate analysis of risk factors. J Pediatr Surg. 1996;31(4):604–6.
18. Kaufman SS, Loseke CA, Lupo JV, et al. Influence of bacterial overgrowth and intestinal inflammation on duration of parenteral nutrition in children with short bowel syndrome. J Pediatr. 1997;131(3):356–61.
19. Bueno J, Ohwada S, Kocoshis S, et al. Factors impacting the survival of children with intestinal failure referred for intestinal transplantation. J Pediatr Surg. 1999;34(1):27–32. discussion 32–23.
20. Goulet O, Baglin-Gobet S, Talbotec C, et al. Outcome and long-term growth after extensive small bowel resection in the neonatal period: a survey of 87 children. Eur J Pediatr Surg. 2005;15(2):95–101.
21. Affourtit MJ, Tibboel D, Hart AE, Hazebroek FW, Molenaar JC. Bowel resection in the neonatal phase of life: short-term and long-term consequences. Z Kinderchir. 1989;44(3):144–7.
22. Galea MH, Holliday H, Carachi R, Kapila L. Short-bowel syndrome: a collective review. J Pediatr Surg. 1992;27(5):592–6.
23. Georgeson KE, Breaux Jr CW. Outcome and intestinal adaptation in neonatal short-bowel syndrome. J Pediatr Surg. 1992;27(3):344–8. discussion 348–350.
24. Teitelbaum DH, Drongowski R, Spivak D. Rapid development of hyperbilirubinemia in infants with the short bowel syndrome as a correlate to mortality: possible indication for early small bowel transplantation. Transplant Proc. 1996;28(5):2699–700.
25. Sax HC. Specific nutrients in intestinal failure: one size fits no one. Gastroenterology. 2006;130(2 Suppl 1):S91–S2.
26. DiBaise JK, Young RJ, Vanderhoof JA. Intestinal rehabilitation and the short bowel syndrome: part 1. Am J Gastroenterol. 2004;99(7):1386–95.
27. Ruiz P, Kato T, Tzakis A. Current status of transplantation of the small intestine. Transplantation. 2007;83(1):1–6.
28. Abu-Elmagd KM. Intestinal transplantation for short bowel syndrome and gastrointestinal failure: current consensus, rewarding outcomes, and practical guidelines. Gastroenterology. 2006;130(2 Suppl 1):S132–S7.
29. Pironi L, Forbes A, Joly F, et al. Survival of patients identified as candidates for intestinal transplantation: a 3-year prospective follow-up. Gastroenterology. 2008;135(1):61–71.
30. Kocoshis SA. Medical management of pediatric intestinal failure. Semin Pediatr Surg. 2010;19(1):20–6.
31. Goulet O, Joly F, Corriol O, Colomb-Jung V. Some new insights in intestinal failure-associated liver disease. Curr Opin Organ Transplant. 2009;14(3):256–61.
32. Shin JI, Namgung R, Park MS, Lee C. Could lipid infusion be a risk for parenteral nutrition-associated cholestasis in low birth weight neonates? Eur J Pediatr. 2008;167(2):197–202.
33. Jeejeebhoy KN. Enteral nutrition versus parenteral nutrition–the risks and benefits. Nat Clin Pract Gastroenterol Hepatol. 2007;4(5):260–5.
34. Gura KM, Lee S, Valim C, et al. Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. Pediatrics. 2008;121(3):e678–e86.
35. Gura KM, Duggan CP, Collier SB, et al. Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. Pediatrics. 2006;118(1):e197–201.
36. Ekema G, Falchetti D, Boroni G, et al. Reversal of severe parenteral nutrition-associated liver disease in an infant with short bowel syndrome using parenteral fish oil (Omega-3 fatty acids). J Pediatr Surg. 2008;43(6):1191–5.
37. Goulet O, Antebi H, Wolf C, et al. A new intravenous fat emulsion containing soybean oil, medium-chain triglycerides, olive oil, and fish oil: a single-center, double-blind randomized study on efficacy and safety in pediatric patients receiving home parenteral nutrition. JPEN J Parenter Enteral Nutr. 2010;34(5):485–95.
38. Putet G, Bresson JL, Ricour C. Exclusive parenteral nutrition in children. Influence of continuous or cyclic intake on the utilization of food. Arch Fr Pediatr. 1984;41(2):111–5.
39. Matuchansky C, Messing B, Jeejeebhoy KN, Beau P, Beliah M, Allard JP. Cyclical parenteral nutrition. Lancet. 1992;340(8819):588–92.
40. Lloyd DA, Gabe SM. Managing liver dysfunction in parenteral nutrition. Proc Nutr Soc. 2007;66(4):530–8.
41. Goulet O, Ruemmele F, Lacaille F, Colomb V. Irreversible intestinal failure. J Pediatr Gastroenterol Nutr. 2004;38(3):250–69.
42. Lentze MJ. Intestinal adaptation in short-bowel syndrome. Eur J Pediatr. 1989;148(4):294–9.
43. Rao JN, Wang JY. Regulation of gastrointestinal mucosal growth. San Rafael, CA: Morgan & Claypool Life Sciences; 2010. 2011/06/03 ed.
44. Tappenden KA. Mechanisms of enteral nutrient-enhanced intestinal adaptation. Gastroenterology. 2006;130 (2 Suppl 1):S93–S9.

45. Alpers DH. Glutamine: do the data support the cause for glutamine supplementation in humans? Gastroenterology. 2006;130(2 Suppl 1):S106–S16.
46. Gouttebel MC, Astre C, Briand D, Saint-Aubert B, Girardot PM, Joyeux H. Influence of N-acetylglutamine or glutamine infusion on plasma amino acid concentrations during the early phase of small-bowel adaptation in the dog. JPEN J Parenter Enteral Nutr. 1992;16(2):117–21.
47. Tamada H, Nezu R, Matsuo Y, Imamura I, Takagi Y, Okada A. Alanyl glutamine-enriched total parenteral nutrition restores intestinal adaptation after either proximal or distal massive resection in rats. JPEN J Parenter Enteral Nutr. 1993;17(3):236–42.
48. Smith RJ, Wilmore DW. Glutamine nutrition and requirements. JPEN J Parenter Enteral Nutr. 1990;14(4 Suppl): 94S–9S.
49. Vanderhoof JA, Blackwood DJ, Mohammadpour H, Park JH. Effects of oral supplementation of glutamine on small intestinal mucosal mass following resection. J Am Coll Nutr. 1992;11(2):223–7.
50. Michail S, Mohammadpour H, Park JH, Vanderhoof JA. Effect of glutamine-supplemented elemental diet on mucosal adaptation following bowel resection in rats. J Pediatr Gastroenterol Nutr. 1995;21(4):394–8.
51. Yang H, Larsson J, Permert J, Braaf Y, Wiren M. No effect of bolus glutamine supplementation on the postresectional adaptation of small bowel mucosa in rats receiving chow ad libitum. Dig Surg. 2000;17(3):256–60.
52. Albers MJ, Steyerberg EW, Hazebroek FW, et al. Glutamine supplementation of parenteral nutrition does not improve intestinal permeability, nitrogen balance, or outcome in newborns and infants undergoing digestive-tract surgery: results from a double-blind, randomized, controlled trial. Ann Surg. 2005;241(4):599–606.
53. Vaughn P, Thomas P, Clark R, Neu J. Enteral glutamine supplementation and morbidity in low birth weight infants. J Pediatr. 2003;142(6):662–8.
54. van den Berg A, van Elburg RM, Westerbeek EA, Twisk JW, Fetter WP. Glutamine-enriched enteral nutrition in very-low-birth-weight infants and effects on feeding tolerance and infectious morbidity: a randomized controlled trial. Am J Clin Nutr. 2005;81(6):1397–404.
55. Scolapio JS, Camilleri M, Fleming CR, et al. Effect of growth hormone, glutamine, and diet on adaptation in short-bowel syndrome: a randomized, controlled study. Gastroenterology. 1997;113(4):1074–81.
56. Szkudlarek J, Jeppesen PB, Mortensen PB. Effect of high dose growth hormone with glutamine and no change in diet on intestinal absorption in short bowel patients: a randomised, double blind, crossover, placebo controlled study. Gut. 2000;47(2):199–205.
57. Scolapio JS, McGreevy K, Tennyson GS, Burnett OL. Effect of glutamine in short-bowel syndrome. Clin Nutr. 2001;20(4):319–23.
58. Beaugerie L, Carbonnel F, Hecketsweiler B, Dechelotte P, Gendre JP, Cosnes J. Effects of an isotonic oral rehydration solution, enriched with glutamine, on fluid and sodium absorption in patients with a short-bowel. Aliment Pharmacol Ther. 1997;11(4):741–6.
59. Scolapio JS. Effect of growth hormone, glutamine, and diet on body composition in short bowel syndrome: a randomized, controlled study. JPEN J Parenter Enteral Nutr. 1999;23(6):309–12. discussion 312–303.
60. Jeppesen PB, Szkudlarek J, Hoy CE, Mortensen PB. Effect of high-dose growth hormone and glutamine on body composition, urine creatinine excretion, fatty acid absorption, and essential fatty acids status in short bowel patients: a randomized, double-blind, crossover, placebo-controlled study. Scand J Gastroenterol. 2001;36(1):48–54.
61. DiBaise JK, Young RJ, Vanderhoof JA. Intestinal rehabilitation and the short bowel syndrome: part 2. Am J Gastroenterol. 2004;99(9):1823–32.
62. Aggett PJ, Agostoni C, Axelsson I, et al. Nondigestible carbohydrates in the diets of infants and young children: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2003;36(3):329–37.
63. Li-Ling IM. The effectiveness of growth hormone, glutamine and a low-fat diet containing high-carbohydrate on the enhancement of the function of remnant intestine among patients with short bowel syndrome: a review of published trials. Clin Nutr. 2001;20(3):199–204.
64. McNeil NI. The contribution of the large intestine to energy supplies in man. Am J Clin Nutr. 1984;39(2):338–42.
65. Roth JA, Frankel WL, Zhang W, Klurfeld DM, Rombeau JL. Pectin improves colonic function in rat short bowel syndrome. J Surg Res. 1995;58(2):240–6.
66. Koruda MJ, Rolandelli RH, Settle RG, Saul SH, Rombeau JL. Harry M. Vars award. The effect of a pectin-supplemented elemental diet on intestinal adaptation to massive small bowel resection. JPEN J Parenter Enteral Nutr. 1986;10(4):343–50.
67. Finkel Y, Brown G, Smith HL, Buchanan E, Booth IW. The effects of a pectin-supplemented elemental diet in a boy with short gut syndrome. Acta Paediatr Scand. 1990;79(10):983–6.
68. Heinig MJ. Host defense benefits of breastfeeding for the infant. Effect of breastfeeding duration and exclusivity. Pediatr Clin North Am. 2001;48(1):105–23. ix.
69. Victora CG, Smith PG, Vaughan JP, et al. Evidence for protection by breast-feeding against infant deaths from infectious diseases in Brazil. Lancet. 1987;2(8554):319–22.

70. Cummins AG, Thompson FM. Effect of breast milk and weaning on epithelial growth of the small intestine in humans. Gut. 2002;51(5):748–54.
71. Playford RJ, Macdonald CE, Johnson WS. Colostrum and milk-derived peptide growth factors for the treatment of gastrointestinal disorders. Am J Clin Nutr. 2000;72(1):5–14.
72. Andorsky DJ, Lund DP, Lillehei CW, et al. Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. J Pediatr. 2001;139(1):27–33.
73. Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. Lancet. 1990;336(8730):1519–23.
74. Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. Pediatrics. 1999;103(6 Pt 1):1150–7.
75. McGuire W, Anthony MY. Donor human milk versus formula for preventing necrotising enterocolitis in preterm infants: systematic review. Arch Dis Child Fetal Neonatal Ed. 2003;88(1):F11–F4.
76. Boyd CA, Quigley MA, Brocklehurst P. Donor breast milk versus infant formula for preterm infants: systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2007;92(3):F169–F75.
77. Henry MC, Moss LR. Necrotizing enterocolitis. Annu Rev Med. 2009;60:111–24.
78. Olieman JF, Tibboel D, Penning C. Growth and nutritional aspects of infantile short bowel syndrome for the past 2 decades. J Pediatr Surg. 2008;43(11):2061–9.
79. Wight NE. Donor human milk for preterm infants. J Perinatol. 2001;21(4):249–54.
80. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ. 2001;323(7308):334–6.
81. Ekingen G, Ceran C, Guvenc BH, Tuzlaci A, Kahraman H. Early enteral feeding in newborn surgical patients. Nutrition. 2005;21(2):142–6.
82. Tyson J, Kennedy K. Minimal enteral feeding for promoting feeding tolerance and preventing morbidity in parenterally fed infants. Cochrane Database Syst Rev. 1997;4:CD000504.
83. Ksiazyk J, Piena M, Kierkus J, Lyszkowska M. Hydrolyzed versus nonhydrolyzed protein diet in short bowel syndrome in children. J Pediatr Gastroenterol Nutr. 2002;35(5):615–8.
84. Vanderhoof JA, Young RJ. Enteral and parenteral nutrition in the care of patients with short-bowel syndrome. Best Pract Res Clin Gastroenterol. 2003;17(6):997–1015.
85. Parker P, Stroop S, Greene H. A controlled comparison of continuous versus intermittent feeding in the treatment of infants with intestinal disease. J Pediatr. 1981;99(3):360–4.
86. Serrano MS, Schmidt-Sommerfeld E. Nutrition support of infants with short bowel syndrome. Nutrition. 2002;18(11–12):966–70.
87. Drenckpohl D, Hocker J, Shareef M, Vegunta R, Colgan C. Adding dietary green beans resolves the diarrhea associated with bowel surgery in neonates: a case study. Nutr Clin Pract. 2005;20(6):674–7.
88. Torres C, Sudan D, Vanderhoof J, et al. Role of an intestinal rehabilitation program in the treatment of advanced intestinal failure. J Pediatr Gastroenterol Nutr. 2007;45(2):204–12.
89. Fishbein TM, Schiano T, LeLeiko N, et al. An integrated approach to intestinal failure: results of a new program with total parenteral nutrition, bowel rehabilitation, and transplantation. J Gastrointest Surg. 2002;6(4):554–62.
90. Nucci A, Burns RC, Armah T, et al. Interdisciplinary management of pediatric intestinal failure: a 10-year review of rehabilitation and transplantation. J Gastrointest Surg. 2008;12(3):429–35. discussion 435–426. Epub 2007 Dec 2018.
91. Modi BP, Langer M, Ching YA, et al. Improved survival in a multidisciplinary short bowel syndrome program. J Pediatr Surg. 2008;43(1):20–4.
92. Diamond IR, de Silva N, Pencharz PB, Kim JH, Wales PW. Neonatal short bowel syndrome outcomes after the establishment of the first Canadian multidisciplinary intestinal rehabilitation program: preliminary experience. J Pediatr Surg. 2007;42(5):806–11.
93. Sudan D, Dibaise J, Torres C, et al. A multidisciplinary approach to the treatment of intestinal failure. J Gastrointest Surg. 2005;9(2):165–77.
94. Modi BP, Javid PJ, Jaksic T, et al. First report of the international serial transverse enteroplasty data registry: indications, efficacy, and complications. J Am Coll Surg. 2007;204(3):365–71.
95. Javid PJ, Collier S, Richardson D, et al. The role of enteral nutrition in the reversal of parenteral nutrition-associated liver dysfunction in infants. J Pediatr Surg. 2005;40(6):1015–8.
96. Teitelbaum DH, Tracy T. Parenteral nutrition-associated cholestasis. Semin Pediatr Surg. 2001;10(2):72–80.
97. Olieman JF, Poley MJ, Gischler SJ, et al. Interdisciplinary management of infantile short bowel syndrome: resource consumption, growth, and nutrition. J Pediatr Surg. 2010;45(3):490–8.
98. Olieman J, Penning C, Spoel M, et al. Long term impact of infantile short bowel syndrome on nutrtional status and growth. Br J Nutr. 2012;107(10):1489–97.

Chapter 5
Percutaneous Endoscopic Gastrostomy

Patricia Davidson and Scott Nightingale

Key Points

- Percutaneous endoscopic gastrostomy is a safe, effective means of maintaining enteral nutrition in the medium to long term in infants and children who are unable to maintain adequate oral nutritional intake.
- Minor complications such as wound infection or erythema and granulation tissue are common and easily treated.
- Serious complications are uncommon and include injury to intra-abdominal viscera during insertion and separation of the stomach from the abdominal wall which may occur when changing the PEG to a low-profile device. Appropriate precautions can minimise the risk of these complications.

Keywords Gastrostomy • Endoscopy • Enteral feeding • Complications • Nutrition

Introduction

Children who are unable to maintain adequate nutrition due to poor oral intake require enteral feeding [1–4]. In this situation, a clinical judgement is usually made between either nasogastric feeds or gastrostomy. The decision hinges on the benefits of a long-term gastrostomy versus the risks of the procedure [5]. Nasogastric feeds are often commenced initially, and a decision to proceed with gastrostomy occurs when it becomes clear that longer-term or permanent enteral feeding is required. The commonest reason for gastrostomy placement in children is neurological disability (congenital or acquired brain injury), followed by other indications such as congenital heart disease, chronic lung disease, cystic fibrosis, congenital malformations that prevent swallowing and malignancy [6, 7].

Gastrostomy can be achieved surgically, laparoscopically, radiologically, or endoscopically. Percutaneous endoscopic gastrostomy (PEG) is widely used as it has the advantage of visualisation of

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the insertion site both internally and externally, requires minimal tissue damage and is relatively safe if performed carefully by an experienced operator. PEG was initially described as a method of gastrostomy placement for children who were unsuitable for laparotomy [8]. Subsequent experience has confirmed that this is a suitable method for insertion of a gastrostomy [9–12]. It is the method of choice if no other intra-abdominal procedure is required.

This chapter details the principles of insertion and emphasises the common problems that may be encountered.

Practice and Procedures

Pre-operative Preparation

Patient Evaluation

In children with gastro-oesophageal reflux, strong consideration should be given to undertaking an anti-reflux procedure at the time of gastrostomy. Evaluation with oesophageal pH or impedance manometry may be helpful in identifying these patients. Pre-operative dysphagia or aspiration on modified barium study was associated with need for further anti-reflux procedure following PEG [7]. Previous surgery may be a contraindication to insertion of a PEG because of the risks of interposition of an organ (usually liver) or viscus (usually colon) between the abdominal wall and the stomach. This complication can still occur without any previous surgery [9]. PEG can be safely performed in small infants [13].

Patient and Caregiver Information

The risks and benefits of the procedure are discussed so that the child and parent/caregiver understand and are able to give informed consent [14]. Post-operative complications are reported in 12–20% of large paediatric series, with most being minor such as wound infection or erythema, or granulation tissue [6, 7, 15]. Careful attention to detail ensures the risks of the procedure are minimised [16]. The parent/caregiver should discuss the details of the feeding regimen with the dietitian and/or nurse to ensure that all additional equipment is available prior to insertion of the PEG, and caregivers know how to use it safely. An opportunity to meet with other parents and children who have a gastrostomy may be beneficial. The impact on caregiving time, family routine and relationships, and attitudes towards gastrostomy feeding should be explored since these can be significant and require specific support [17]. Written information about PEG care and troubleshooting should be provided, and an accessible contact person for problems, such as an experienced nurse should be identified.

Nutritional Requirements

The feeding regimen should be chosen beforehand so that this can be implemented once the PEG is in situ. Involvement of a dietician is important to ensure that energy, macronutrient and micronutrient needs of the child are met. Alternatives include infant formula, liquid enteral feeds, and ordinary food processed in a blender. This decision influences the size of the PEG inserted. If a child is to receive continuous feeds a feeding pump is needed.

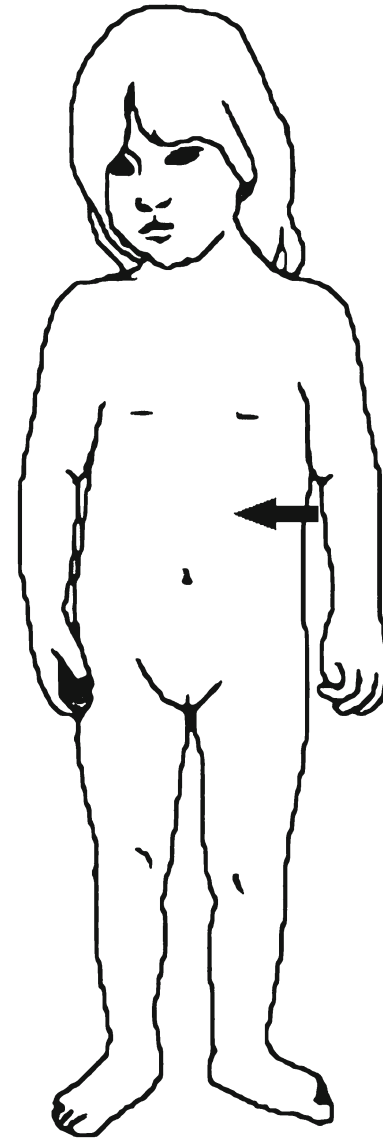

Fig. 5.1 Insertion site of the PEG

Fasting and Wound Site Preparation

The children should be fasted for the time consistent with local hospital practice. Pre-operative antibiotic prophylaxis has been shown in meta-analyses of randomised trials to significantly reduce post-operative wound infections (number needed to treat of 8), with penicillin and cephalosporin antibiotics having similar efficacy [18]. The site for insertion of the PEG is selected pre-operatively and marked on the anterior abdominal wall. This position is normally mid-way between the umbilicus and the costal margin in the mid-clavicular line (Fig. 5.1). Preparation of the skin with an iodine-containing solution just prior to departure for the operating suite may minimise the risks of wound infection.

Operating Room Procedure Instruments Required

There are a large number of PEG kits available that include all the instruments necessary for insertion. The contents include: a PEG feeding tube with internal bumper and external bolsters, a trocar with removable stylet, a flexible-tipped guide wire, syringe, needle, and scalpel. The PEG kit that is used depends on the size of the child, the dimension requirements for the gastrostomy and the choice of the operator. The selected PEG catheter should be immersed in an iodine-containing solution prior to insertion to minimise post-operative wound infections. Paediatric endoscopes, with accompanying snare or forceps, and an a-septic trolley, with equipment for skin preparation and draping, are required.

Method of Anaesthesia

Opinions regarding the most appropriate technique by which a patient can achieve both adequate pain relief and a lack of awareness of the procedure are divided. Options include deep intravenous sedation or general anaesthetic. Either method should include local anaesthetic at the site of the PEG to provide post-operative pain relief. The patient's needs and experience of the staff involved determine which method is chosen.

Operative Technique

Insertion of a PEG requires two operators: one to perform the endoscopy (the endoscopist) and one gloved in an aseptic manner (surgeon) to prepare the abdominal wall and insert the trocar. The procedure can be performed by one operator but is more time-consuming and difficult. Once in the operating room with the child placed in the supine position, the endoscopist performs a routine upper gastrointestinal endoscopy with biopsies of oesophagus, stomach and duodenum to confirm the presence of normal anatomy and to identify any additional abnormalities (e.g. oesophagitis). Then the stomach is inflated with air to ensure that it approximates to the anterior abdominal wall. At the same time, the surgeon prepares the abdominal wall with an iodine-containing solution. The anticipated site for the PEG is identified by the surgeon pressing down with an index finger at the site for insertion. This produces an indentation on the anterior aspect of the stomach that is clearly visible to the endoscopist. The tip of the flexible endoscope is directed towards this site. The bright light from the endoscope should be clearly visible transilluminating the abdominal wall at the prospective site of the insertion. If not, dim the operating room lights to allow the light to be seen more easily. If the indentation caused by the index finger of the surgeon is not visible and/or if transillumination suggests an interposed viscus or organ an alternative site should be chosen or the gastrostomy should be inserted by the open technique. If proceeding with a PEG infiltrate the site with local anaesthetic. Make a small incision in the skin and introduce the trocar into the stomach. This is accompanied by a 'pop' as the trocar enters the stomach. The tip of the trocar should be visible through the endoscope. If it is not, it may be lying within the peritoneal cavity. The trocar should then be removed and a second attempt made to introduce it into the stomach. Multiple insertions should not be attempted because of the risks of leakage of gastric contents or pneumoperitoneum. Once successful the stylet is removed and a flexible-tipped guide wire is passed into the stomach. It is important to keep the stomach inflated with air during this time, as there is a tendency for it to deflate once the stylet is removed from the trocar. The guide wire is then retrieved, either with an endoscopic snare or forceps and then withdrawn through the oesophagus and mouth. The trocar is removed from the anterior abdominal wall. The tip of the PEG catheter is pushed over, or attached to, the guide wire and pulled down into the stomach and out through the abdominal wall (Fig. 5.2).

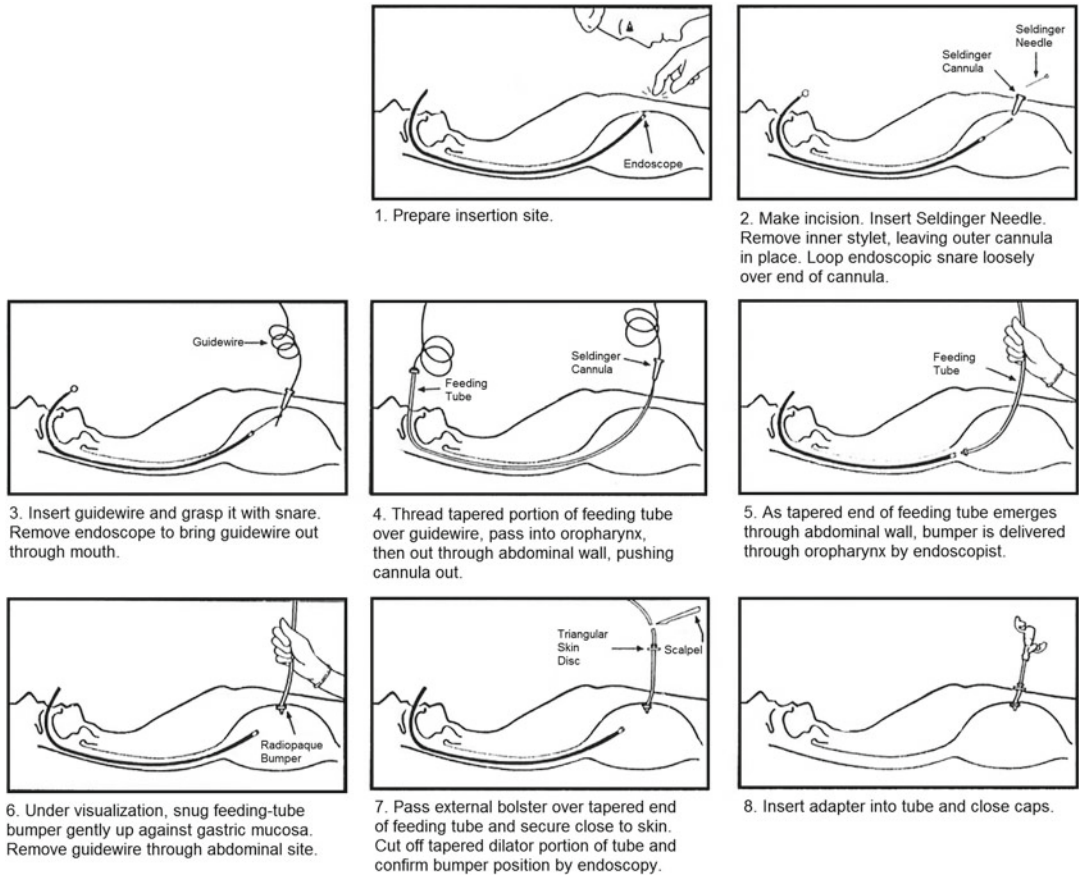

Fig. 5.2 Overview of operative technique

The endoscope is returned to the stomach and the internal bumper of the PEG catheter is visualised. It should lie comfortably against the gastric mucosa. The external bolster is placed against the skin to ensure the PEG catheter is retained in position. The bolster should not be too tightly applied as this leads to skin and gastric mucosal ischaemia predisposing to infection at the site of insertion. The endoscope is removed at completion of the procedure.

Post-operative Care

The PEG can be used early after insertion, with no increase in complications when used ≤3 h of insertion compared to delayed use [19]. A crystalloid solution is often used initially, and allows appropriate fluid balance to be maintained in the immediate post-operative period, before changing to the desired feed. The patient should avoid oral intake in the early post-operative period until the PEG is functioning without complication.

Despite the smaller incision required for insertion of a PEG, the wound is often painful post-operatively. After the local anaesthetic has ceased to provide pain relief, provision should be made for administration of adequate analgesia. Opiates, as an intravenous infusion may be required during the first 24 h.

Once the patient is stable and recovered from the anaesthetic, a regime of gastrostomy feeds can be commenced. Parents need instruction on use of the catheter and how to vent the catheter in the event of gastric dilatation. Parents and or the patient should be given instructions on meticulous cleaning of the PEG catheter around the insertion site. This helps prevent wound infection and subsequent granuloma formation. The feeding catheter must be rotated at regular intervals (daily for two weeks) to maintain mobility within the gastrostomy. This helps prevent submucosal migration of the internal bumper.

The PEG may be replaced by a low-profile device when the stomach has adhered firmly to the abdominal wall, typically after 3–6 months. The highest risk of separation of the stomach from the abdominal wall occurs at the time of the first change from PEG to low-profile device. It is recommended that this occurs under endoscopic vision.

Discussion

Common Problems and Possible Solutions

Operative and Early Post-operative Problems (Within 6 h)

- *Difficulty in manipulating the tip of the endoscope directly underneath the site selected for insertion of the PEG*: once a 'j' shape is obtained, rotation of the endoscope often brings the tip around to the position required. Insertion of too great a length of the endoscope adversely affects the position.
- *Failure to introduce the trocar into the stomach*: this results in a false passage into the peritoneum. Make sure the stomach is fully inflated against the abdominal wall. Ensure that the trocar is introduced at an angle pointing slightly upwards and towards the xiphisternum. A firm sharp push ensures puncture of the stomach rather than allowing the tip of the trocar to deflect off the external stomach wall.
- *Difficulty passing the PEG catheter through the oesophagus*: this occurs particularly in smaller children. Ensure that the guide wire runs freely, flexible tip first, and that the external diameter of the PEG catheter selected is not too great for the oesophagus.
- *Interposed viscus or organ*: this can be avoided by ensuring that the indentation caused by an index finger is clearly visible and that no tissue is visible on transillumination of the abdomen.
- *Post-operative bleeding*: the superior epigastric artery can be visualised by transillumination of the abdomen and should be avoided; multiple passes with the trocar should not be performed.
- *Surgical emphysema or pneumoperitoneum*: persistent surgical emphysema or pneumoperitoneum suggests perforation of a viscus. If the distance between the internal bumper and the external bolster is greater than the anticipated depth of the abdominal wall this supports interposition of a viscus.
- *Post-operative pain*: local anaesthetic should be instilled in the wound pre-operatively and adequate post-operative analgesia should be prescribed (Table 5.1).

Post-operative Problems (1 week)

- *Post-operative wound infection*: the risk of this complication can be minimised with routine pre-operative antibiotic prophylaxis, aseptic preparation of the abdominal wall during insertion, antiseptic coating of the PEG catheter with an iodine solution, and by avoiding excessive pressure between the internal and external components of the PEG. Treatment of established infections,

Table 5.1 Common problems and possible solutions with the percutaneous gastrostomy technique

Problem	Action
Identifying correct site for PEG	Check for interposed viscus or organ
	Position endoscope in 'j' shape and rotate endoscope
	Avoid inserting too much endoscope
Failure to introduce trocar into stomach	Fully inflate stomach
	Angle trocar towards xiphisternum
	Push trocar firmly into stomach
Post-operative wound infection	Antibiotic prophylaxis
	Soak catheter in iodine-containing solution
	Avoid tension under the external bolster
Granulation tissue at PEG site	Frequent local cleaning with iodine-containing solution
	Topical application of paw-paw ointment or 1% hydrocortisone cream
	Cautery to granulation tissue
Leakage around PEG	Treat granulation tissue
	Decrease feeding rate
PEG catheter submucosal migration	Rotate catheter daily for 2 weeks
PEG catheter migration with gastric outlet obstruction	Withdraw and reposition PEG catheter comfortably adjacent to stomach wall (1–2 cm)
PEG catheter extrusion	Treat wound infection if necessary; remove PEG catheter and replace with another

which are often due to skin organisms, may require intravenous antibiotics and should be guided by microbiological culture of wound swabs.

- *Submucosal migration of the internal bumper*: the risk of this complication can be reduced by rotating the PEG catheter daily for 2 weeks after insertion. If established, it may require removal and device reinsertion.

Late Post-operative Problems (Weeks or Months Later)

- *Granulation tissue at the site of the PEG*: granulation tissue forms where tissue healing is prolonged, and may be painful, or lead to bleeding. Factors that may contribute to this are friction from the device being too loose, excessive leakage, or a foreign body reaction to the device itself. After correcting contributing factors, granulation tissue can be treated with careful direct application of silver nitrate, paw-paw ointment or topical corticosteroid such as hydrocortisone or triamcinolone cream.
- *Leakage around the PEG catheter*: this may be due to granulation tissue (see above) or if a poor-fitting low-profile device has been inserted. It is unusual with a PEG, and rarely may be due to damage to the PEG itself.
- *PEG catheter extrusion*: this may occur with accidental traction, particularly in the setting of infection. It is important that a device is replaced as soon as possible so that the tract does not close spontaneously (can occur rapidly particularly if the PEG has been inserted within the previous 6 weeks). Parents should be supplied with a replacement catheter of appropriate size so that this can be inserted to maintain the patency of the tract until definitive replacement can occur. If within the first 6 weeks of PEG, when there is a risk of separation of the stomach and abdominal wall with tube reinsertion, this should only be attempted by an experienced practitioner.
- *PEG catheter migration*: the catheter can migrate internally if the external bolster slips. Complications include obstruction of the pylorus. The tube should be pulled back and bolster re-positioned.

- *Gastro-oesophageal reflux*: ideally this is identified prior to PEG placement, but it may develop *de novo* following PEG. There is a lack of prospective paediatric studies to address the relationship between PEG and reflux, with conflicting retrospective data. This does seem to be more likely in children with neurological disability, or with large bolus feeds. Management options include anti-secretory or prokinetic medications, jejunal feeding or surgical anti-reflux procedures.

Conclusion

PEG is a simple and effective method of securing long-term access for enteral feeding in children who cannot maintain necessary oral intake. With careful attention to pre-, intra-, and post-operative care, it is very safe.

References

1. Moore MC, Greene HL. Tube feeding of infants and children. Pediatr Clin North Am. 1985;32:401–17.
2. Goulet O. Enteral feeding in children. Rev Prat. 1991;41:703–9.
3. Amundson JA, et al. Early identification and treatment necessary to prevent malnutrition in children and adolescents with severe disabilities. J Am Diet Assoc. 1994;94:880–3.
4. Heine RG, Reddihough DS, Catto-Smith AG. Gastro-oesophageal reflux and feeding problems after gastrostomy in children with severe neurological impairment. Dev Med Child Neurol. 1995;37:320–9.
5. Rabeneck L, McCullough LB, Wray NP. Ethically justified, clinically comprehensive guidelines for percutaneous endoscopic gastrostomy tube placement. Lancet. 1997;349:496–8.
6. Srinivasan R, Irvine T, Dalzell M. Indications for percutaneous endoscopic gastrostomy and procedure-related outcome. J Pediatr Gastroenterol Nutr. 2009;49:584–8.
7. Fortunato JE, et al. Outcome after percutaneous endoscopic gastrostomy in children and young adults. J Pediatr Gastroenterol Nutr. 2010;50:390–3.
8. Gauderer MWL, Ponsky JL, Izant RJ. Gastrostomy without laparotomy: A percutaneous endoscopic technique. J Paediatr Surg. 1980;15:872–5.
9. Coughlin JP, Gauderer MWL, Stellato TA. Percutaneous gastrostomy in children under 1 year of age: Indications, complications and outcome. Pediatr Surg Int. 1991;6:88–91.
10. Gauderer MWL. Percutaneous endoscopic gastrostomy: A 1 year experience with children. J Pediatr Surg. 1991;26:288–92.
11. Davidson PM, Catto-Smith AG, Beasley SW. Technique and complications of percutaneous endoscopic gastrostomy in children. ANZ J Surg. 1994;65:194–6.
12. Marin OE, et al. Safety and efficacy of percutaneous endoscopic gastrostomy in children. Am J Gastroenterol. 1994;89:357–61.
13. Wilson L, Oliva-Hemker M. Percutaneous endoscopic gastrostomy in small medically complex infants. Endoscopy. 2001;33:433–6.
14. Huddleston KC, Ferraro AR. Preparing families of children with gastrostomies. Pediatr Nurs. 1991;17:153–8.
15. Fox VL, Abel SD, Malas S, et al. Complications following percutaneous endoscopic gastrostomy and subsequent catheter replacement in children and young adults. Gastrointest Endosc. 1997;45:64–71.
16. Beasley SW, Davidson PM, Catto-Smith AG. How to avoid complications during percutaneous endoscopic gastrostomy. J Paediatr Surg. 1995;3:671–3.
17. Brotherton AM, Abbott J, Aggett PJ. The impact of percutaneous endoscopic gastrostomy feeding in children; the parental perspective. Child Care Health Dev. 2007;33:539–46.
18. Jafri NS, Mahid SS, Minor KS, Idstein SR, Hornung CA, Galandiuk S. Meta-analysis: Antibiotic prophylaxis to prevent peristomal infection following percutaneous endoscopic gastrostomy. Aliment Pharmacol Ther. 2007;25:647–56.
19. Szary NM, Arif M, Matteson ML, Choudhary A, Puli SR, Bechtold ML. Enteral feeding within three hours after percutaneous endoscopic gastrostomy placement: a meta-analysis. J Clin Gastroenterol. 2011;45:e34–8.

Chapter 6
Nutritional Support in Crohn's Disease

Anthony E. Wiskin and R. Mark Beattie

Key Points

- 25% of Crohn's disease presents in childhood and may present with a variety of symptoms.
- Poor growth can be the only presenting feature.
- Nutritional impairment at diagnosis can be quite profound, and may include severe malnutrition.
- Nutritional intervention alone (exclusive enteral nutrition—EEN) can reduce clinical symptoms, improve biochemical markers of inflammation and resolve mucosal inflammation.
- EEN is not suitable for all children; however children receiving other treatments are likely to need adjuvant nutritional support

Keywords Nutrition • Exclusive enteral nutrition • Crohn's disease • Paediatrics • Inflammation

Nutritional Support in Crohn's Disease

Crohn's disease is characterised by transmural inflammation located at any point within the gastrointestinal tract from mouth to anus. Crohn's disease is diagnosed by histological findings in individuals with compatible clinical history and examination. The hallmark feature of Crohn's is discontinuous inflammation with associated non-caseating granulomata.

Up to 30% of Crohn's disease is diagnosed before the age of 20 years [1] with an incidence of approximately 3 per 100,000 children aged under 16 years [2]. It is a lifelong condition and typically follows a chronic relapsing disease course. Symptoms depend on disease location. Small bowel disease tends to give vague symptoms of abdominal pain, poor appetite and lethargy. Colonic disease is associated with bloody diarrhoea and pain prior to defecation. Many children are often short for their age and underweight for their height, particularly at diagnosis. These deficits can persist into adulthood if children fail to adequately "catch up" with periods of increased height and weight velocity.

The classical triad of presenting features are abdominal pain, diarrhoea and weight loss. In the British Paediatric Surveillance Unit survey this triad was seen in only 25% of children [3] (Fig. 6.1).

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Fig. 6.1 Features of Crohn's disease at diagnosis [3]. With permission from Archives of Disease in Childhood

Table 1 Presenting symptoms and signs

	CD (n = 379)
Common symptoms	
Abdominal pain	274 (72%)
Diarrhoea	214 (56%)
Bleeding	84 (22%)
Weight loss	220 (58%)
Lethargy	103 (27%)
Anorexia	94 (25%)
Other symptoms	
Arthropathy	28
Nausea/vomiting	22
Constipation/soiling	4
Psychiatric symptoms	3
Secondary amenorrhoea	1
Signs	
Anal fistula	17
Growth failure/delayed puberty	14
Anal abscess, ulcer	8
Erythema nodosum/rash	6
Liver disease	3
Appendicectomy	2
Toxic megacolon	

Abdominal pain was the commonest symptom occurring in 75%, nearly 60% had weight loss preceding diagnosis, 56% of children had diarrhoea while only 45% reported both diarrhoea and weight loss. The median age of onset of symptoms was 11.8 years with median age at diagnosis of 12.9 years. The presence of symptoms such as abdominal pain, weight loss, diarrhoea, fever, nausea, aching joints and vomiting that are recurrent (>2 episodes in 6 months) or persistent (>4 weeks) should raise the suspicion of inflammatory bowel disease [4]

Crohn's disease is a clinicopathological diagnosis. Further investigation includes gastroscopy, ileocolonoscopy and small bowel radiology. Other than history and examination several markers are of use to clinicians to determine which children require endoscopy. These include acute phase reactants such as C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR) and platelet count, which in keeping with chronic inflammation are generally raised; haemoglobin and albumin which are often low reflecting persisting inflammation and/or poor nutrition; and raised markers of intestinal inflammation such as faecal calprotectin and lactoferrin. Imaging techniques such as contrast radiology, abdominal ultrasound and more recently magnetic resonance enteroclysis are helpful at identifying areas of bowel thickening suggestive of inflammation and strictured areas which can either be inflammatory or fibrotic.

Nutritional Deficits

The aetiology of poor nutrition in children with Crohn's disease is multifactorial [5] (Fig. 6.2). Poor intake, altered metabolism and nutrient requirements, and increased nutrient losses from the gut may all play a part. Fundamental to this process is the impact of the inflammatory response.

Height

A decline in height SDS during the 5 years preceding diagnosis with Crohn's has been demonstrated using growth records recorded throughout childhood [6]. Only 12% of children maintain a normal

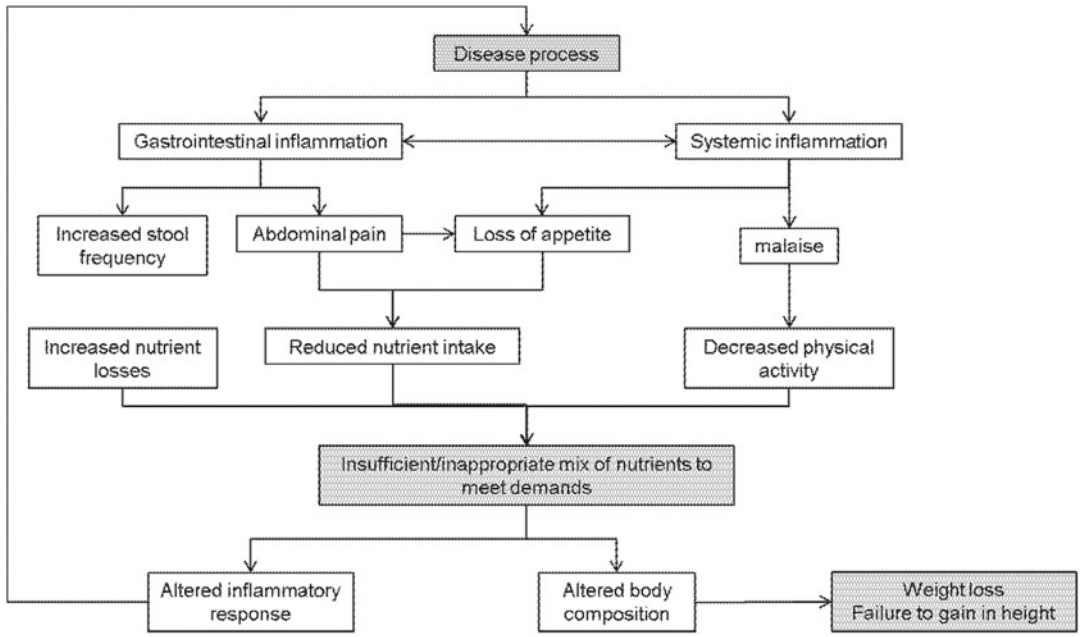

Fig. 6.2 Aetiology of poor nutrition in Crohn's disease

height velocity up to diagnosis [7] and in approximately 40% of patients a decrease in height velocity is found before the onset of gastro-intestinal symptoms. This demonstrates a disparity between overt symptoms of disease and anthropometric changes.

At diagnosis stunting is not unusual; height SDS <−2 has been shown in approximately 10% of children [8, 9] but this does not always resolve with treatment. In one cohort 7% of children 6 years after diagnosis had height SDS <−2 [9]. Retrospective cohort studies demonstrate that between 20 and 85% of children fail to achieve satisfactory adult height [10, 11] although growth can continue into the late teens.

Weight and BMI

Weight loss occurs in approximately 58% of children with Crohn's at diagnosis [3] and significant weight deficits (SDS <−2) are found in 30% [9]. As weight deficits are more profound than height deficits, abnormalities in weight for height SDS or BMI for age SDS are more marked than deficits in weight or height alone [6]. These deficits also persist with treatment and in the cohort reported by Vasseur, 15% of children under follow-up had BMI SDS <−2 [9]. Overweight has also been reported in children with Crohn's disease. Data from the ImproveCareNow Collaborative has shown that nearly 20% of children with Crohn's are overweight or obese (BMI > 85th centile) [12]. However in the USA the prevalence of overweight/obesity in children with Crohn's at diagnosis is not as high as the general population [13].

Body Composition

Measurements of lean mass for age have been reported in several studies using a variety of methods [14, 15] although these measurements are not always adjusted for height. A child could appear to have

a low lean mass simply because they are short; therefore height is an important confounder which does require consideration. Thayu et al., found reduced lean mass for height SDS in both boys and girls but the deficits were more profound in girls [16]. In studies of children under follow-up there is a suggestion that lean mass is reduced more than fat mass [17–19] and that the low lean mass SDS found at diagnosis persists during treatment [15] despite some initial improvements in the first 6 months [20]. The influence corticosteroids have on body composition in these children is unclear. Setongo found that changes in fat mass were associated with steroid exposure [19] while other studies have found no such association [14, 18, 20]. It is of interest that cumulative markers of disease activity have shown no association with lean mass for height SDS [18]. Lean mass deficit may be related to disease activity [21] but it appears that it may not always correct with treatment of the underlying disease. The factors implicated in this deficit are not clearly described. Understanding the mechanisms for these changes may lead to better interventions to promote more healthy patterns of growth.

Adequate lean mass, especially muscle mass, is important for the development of bone mineral density in childhood. Bone is an important constituent of fat free mass. Osteopenia and osteoporosis are common problems in children and adults with Crohn's disease. Vertebral fractures secondary to osteoporosis can occur, even in children who have not received corticosteroids. Assessment of bone density in childhood requires correction for reduced bone mass which may in part be due to poor linear growth. Alterations of the standard used can change the prevalence of osteopenia from 65 to 22% [22]. However, studies suggest that deficits in cortical bone detected at diagnosis persist in children despite treatment, while trabecular bone deficits improve but are not resolved [20].

Micronutrients

Multiple micronutrient or trace element deficiencies have been reported in children and adults with Crohn's disease. Many of these trace elements are either positive or negative acute phase reactants and so measurement during times of active disease must be interpreted with caution. However some studies have shown deficits of nutrients even in disease remission [23]. One of the more widely studied micronutrients is iron. In paediatric cohorts iron deficiency is thought to be responsible for between 40% [24] and 88% [25] of the cases of anaemia in children with Inflammatory Bowel Disease which in turn has a prevalence ranging from 41% [24] to 70% [25].

Nutritional Treatment

It is remarkable that remission in Crohn's disease can be achieved by a combination of bowel rest and provision of suitable nutrients. Exclusive enteral nutrition (EEN) is the administration of either a polymeric or elemental low residue feed as sole nutrient intake for 6–8 weeks. The patient is allowed water to satisfy thirst, but does not eat anything else. Both parenteral nutrition (PN) and EEN therapy have been shown to improve symptoms of Crohn's disease and downregulate the immune response [26, 27]. How these routes of nutrition administration work to achieve reduction in inflammation is unclear. In vitro studies suggest that provision of nutrients to cell cultures improve intestinal barrier function and alter the activation of mononuclear cells [28]. Other work shows a decrease in cytokine production in gut mucosa of patients receiving EEN [29]. Bacteria within faecal effluent are implicated in the pathogenesis of Crohn's and it has been shown that EEN alters gut flora alongside improvements in disease activity with effects lasting longer than the treatment period itself [30].

Exclusive Enteral Nutrition

The use of EEN as treatment for Crohn's was first reported in adult series [31, 32]. By the middle of the 1980s, EEN was widely used in the UK as primary therapy in children with Crohn's and has subsequently been demonstrated to induce endoscopic and histological remission [33]. Meta-analysis of six trials (five in adult populations) that included 192 patients treated with enteral nutrition and 160 treated with steroids favoured steroid therapy [34]. However, the single paediatric study in this meta-analysis showed equal efficacy of EEN to steroids but clear benefits in mucosal healing in favour of the EEN group [35]. A meta-analysis of 144 children with Crohn's found no difference in remission rates at 8–10 weeks in those treated with EEN compared to steroids. In addition two randomised controlled trials of EEN vs. corticosteroids demonstrate clear benefits in linear growth for those receiving EEN [36, 37]. However partial enteral nutrition (50% of calories as EN) does not have the same benefits as EEN [38]. For some time there was debate whether EEN using elemental formula (comprised of amino acids) was of greater benefit than EEN using polymeric (whole protein) formula. Meta-analysis of ten trials comprising 334 patients has demonstrated no difference in the efficacy of elemental vs. non-elemental formulas [34].

One commonly encountered clinical question is whether the remission achieved with EEN is as long lasting as remission achieved by corticosteroids. Over the first year relapse rates are similar in children who receive EEN compared to steroids [39]. Over 5 years of follow-up time to first relapse has been shown to be shorter in children treated with EEN compared to steroids; however these children received a very short EEN course of only 3 weeks [40]. In a retrospectively studied cohort of 40 children who responded to EEN, 25 relapsed with a median duration of remission of 54.5 months [41].

Following the success of EEN as a treatment of active Crohn's disease the role of EN as maintenance therapy has been explored. One randomised controlled trial compared partial EEN (half daily allowance of calories as elemental feed) to free diet in a group of adults with Crohn's concurrently receiving Mesalazine who had achieved remission by TPN, EEN, infliximab or corticosteroids. This study was stopped early as rate of relapse was significantly higher in those on free diet [42]. This observation is supported by another adult cohort where 48% of those on maintenance EEN remained in remission at 12 months compared to 22% who did not [43]. In children Wilschanski et al. found higher relapse rate at 12 months in those who decided not to continue EEN after obtaining remission compared to those who continued a nocturnal EEN feed [44]. In addition Verma et al. demonstrated a reduced steroid requirement in adults with steroid-dependent disease remission who had concurrent partial EN [45]. However in clinical practice, maintaining 50% of calorie intake as EN over the course of 1 year is hard to achieve.

Recent research has examined the role of EN as adjunctive therapy to other treatments particularly infliximab. Tanka demonstrated greater improvements in the disease score in those treated with partial EN and infliximab over 16 weeks for active disease compared to those treated with infliximab alone [46]. However a retrospective study found no difference in efficacy [47]. Similarly those in disease remission on maintenance infliximab had no difference in rate of relapse over 56 weeks whether they received concurrent partial EN or not [48].

Parenteral Nutrition

Initial reports of the utility of parenteral nutrition as primary therapy for Crohn's disease were mixed, possibly reflecting several cohorts which contained Crohn's and Ulcerative Colitis patients. Ten years of PN experience was described by one centre in 1978. They found that almost 40% of patients with refractory disease responded to PN and that 43% of fistulae closed spontaneously while on PN [49].

However PN was not widely accepted as primary therapy because of the complexity of administration and the fact that relapse rates were felt to be higher than conventional treatment [50]. PN was however shown to reduce the need for urgent surgery when used alongside other treatments for acute severe colitis [51]. Currently the use of parenteral nutrition is restricted to those unable to tolerate enteral feed and those who require peri-operative nutrition support.

Clinical Practice

Nutritional Assessment

Prior to initiation of nutritional therapy a thorough investigation of disease activity and extent should be performed. In addition a nutritional assessment should be completed. A dietary history including history of weight loss helps to identify the extent and duration of poor dietary intake. In combination with a physical assessment this will give clues to the likelihood of re-feeding syndrome which has been described in children with Crohn's disease receiving EEN [52]. Those with minimal intake for 5 days, significant weight loss or low serum potassium/phosphate should be considered at risk of re-feeding syndrome and should have feed introduced gradually with biochemical monitoring [53]. Height and weight should be documented and plotted on relevant growth charts. Ideally assessment of fat and fat free mass should be performed either by skinfolds or bioelectrical impedance. DXA should be considered. Interpretation of all body composition measures requires an assessment of pubertal status. Careful evaluation of the effect of the nutritional intervention is desirable to allow tailoring of the prescription to the individual and to avoid increasing adiposity. In order to do this regular assessment of height and weight coupled with measures of fat and fat free mass should be ongoing. Evaluation of changes in appetite and physical activity is helpful to ensure adequate prescription of calories, nutrients and micronutrients.

Exclusive Enteral Nutrition

Who Should Receive EN?

There is a lack of evidence on disease location and the efficacy of EEN as primary therapy, particularly in relation to isolated colonic disease where studies show a lack of concordance [44, 54]. In practice EEN is used widely in children with ileal disease seen at endoscopy regardless of the presence of colonic disease. Children with marked nutritional deficit regardless of disease location are also likely to benefit from EEN as adjunctive therapy to help achieve appropriate nutritional restitution and facilitate "catch up growth" alongside disease remission.

Treatment Regimen

As primary therapy the dose of EEN should be tailored to the individual patient. Initial prescription can be made from Estimates of Average Requirements from dietary reference manuals, or from measurements of resting energy expenditure and physical activity. In practice 100–120% of the requirement is given with increasing amounts as physical activity levels increase. If the risk of re-feeding syndrome is thought to be high a starting dose of 50% of requirement may be used and gradually increased to the full amount with monitoring of serum electrolytes and body weight.

Treatment courses of EEN lasting between 4 and 8 weeks have been used as primary therapy in research studies although no definitive study has been performed to identify optimum treatment

duration. A 6–8-week course of six drinks daily is widely used. In practice, children feel initial benefits of treatment within the first week which helps motivate them to continue. Improvement in inflammatory markers usually occurs within 2 weeks [27]. If the child does respond then the course should be continued until symptoms resolve completely even if that is longer than 8 weeks. The vast majority of children tolerate EEN by mouth. Palatability is improved by using a variety of sugar-free flavourings and ensuring that drinks are kept cold. A number of children prefer to have EEN administered via a naso-gastric tube with feeds given by bolus.

Food Re-introduction

Phased food re-introduction begins at the end of the treatment course and takes approximately 2–4 weeks to complete. During this period enteral nutrition is gradually weaned to ensure nutritional requirements are met. In our centre 4 stages are progressed through each lasting 5 days. Stage 1 introduces plain, low fibre foods such as fish or chicken, but is dairy and wheat free; children usually drop one drink of EEN. Stage 2 permits wheat, but remains dairy free. EEN is reduced to three drinks daily. In Stage 3 dairy is introduced; over 5 days children progress from cooked hidden dairy (cakes and biscuits) through chocolate and cheese to milk alone. Stage 4 liberates the diet to everything the family normally eat. If children develop symptoms such as abdominal pain or nausea, they return to the previous stage of food re-introduction at which they had no problems and then try again after another 5 days have elapsed. In our experience food intolerance is rare during return to normal diet. If problems are found they are more likely to be a general problem, potentially associated with early disease relapse than a response to a specific food group. Children with profound deficits in height or weight at diagnosis are encouraged to continue some EN (2–3 drinks daily) for several months in addition to normal diet to help facilitate "catch up" growth. A multi-disciplinary team approach is integral to the success of EEN treatment with input from dieticians, specialist nurses and physicians.

When EEN Does not Work

Children usually feel a clinical improvement from EEN during the first week of treatment. If this does not occur and the symptoms the child had at presentation do not settle, then the child should be started on an alternative treatment. Even in children whose disease location would suggest that EEN should work, it is important to recognise that up to 20% may not respond. However the child may still benefit from nutritional support in order to facilitate nutritional restitution and growth.

Another indicator of whether therapy is effective is weight gain. While malnourished children may initially lose weight with treatment as fluid is redistributed within body compartments, most children will start to gain weight within the first 10 days of treatment. If not and EEN does appear to be working then poor weight gain may be due to inadequate intake, which may be due to poor compliance, inadequate prescription or poor tolerance of the feed. Each of these issues requires specific intervention from members of the multi-disciplinary team.

Alternative Therapeutic Options

Induction of Remission

In the UK treatment of children with Crohn's follows national [55] and European guidelines [56]. Corticosteroids are the main alternative to EEN for establishing disease remission. Intravenous

hydrocortisone is used for more severe cases while oral prednisolone is most widely used. Budesonide is effective in some cases with less systemic toxicity [57] but its use is not widespread. Intravenous hydrocortisone is given for 3–5 days before converting to oral prednisolone providing there has been symptomatic and biochemical improvement. Oral prednisolone is started at a high dose (2 mg/kg, max 40 mg) for 1–4 weeks before tapering the dose over 4–8 weeks depending on the response. Children being treated with steroids should have adequate dietary intake of calcium and vitamin D therefore supplements may be required. In addition acid suppression may be needed in children with Crohn's disease involving the upper gastro-intestinal tract. In children with more resistant disease who have failed to respond to EEN and/or corticosteroids other alternatives include thiopurines, biologics or surgery.

A recent meta-analysis examined the use of Azathioprine or 6 mercaptopurine for induction of remission in Crohn's [58]. Eight studies of adult patients were included. The authors concluded that these drugs were successful in treating active disease with a number needed to treat (NNT) of 5. The NNT to observe one adverse effect of therapy (fever, leukopenia, pancreatitis, nausea) in a patient is 14. It is recommended to measure thiopurine methyl-transferase (TPMT) activity prior to initiating treatment. About 10% of individuals have low to intermediate levels of TPMT activity and are therefore thought to be at increased risk of immuno-suppression from myelotoxicity.

Methotrexate is not commonly used; however there is some evidence that administration by weekly intra-muscular injections may be of benefit in patients resistant to treatment with corticosteroids [59].

Infliximab is a mono-clonal antibody against tumour necrosis factor alpha, 75% of the antibody is derived from human IgG and the rest from murine sources. In the REACH study, children with Crohn's who had active disease despite treatment with azathioprine or other immunomodulator received infliximab by intravenous infusion at 0, 2 and 6 weeks. At 10 weeks 99 of 103 children had shown clinical improvement with 66 found to be in clinical remission [60]. Pre-treatment screening for exposure to tuberculosis is important as infliximab therapy is associated with increased risk. As a minimum a clinical history and chest X-ray should be performed. The formation of antibodies to infliximab may trigger acute infusion reactions and delayed onset reactions and a dose of hydrocortisone with each infusion may minimise this. The largest concern with infliximab is the risk of malignancy particularly that of hepato-splenic t cell lymphoma which although rare is usually fatal. It is unclear whether this is related to life time exposure to the drug and therefore if children are at increased risk. Adalimumab is a mono-clonal antibody against tumour necrosis factor alpha but is entirely human in origin and is administered by sub-cutaneous rather than intra-venous injection. It is currently used in children who exhibit poor response to infliximab.

Surgery is still felt to be the last resort for treatment of Crohn's disease in childhood; however it can be very effective with minimal adverse events. It is not widely used in children at induction of remission and is usually reserved for those with complications such as fistulae or abscess. In refractory disease significant catch-up growth after surgery in adolescents is well recognised [61, 62] although the recurrence risk is high.

Maintenance of Remission

Close follow-up of children including regular growth monitoring is required to ensure that disease remains controlled after induction of remission. There is no place for corticosteroids as maintenance therapy and there is very limited evidence to support the use of aminosalicylates for maintenance of remission [63]. The efficacy of thiopurines was confirmed by meta-analysis of seven studies which demonstrated an NNT of 6 for azathioprine to maintain disease remission [64]. Azathioprine and 6 mercaptopurine (6MP) are the most widely used agents in paediatric IBD. Regular blood monitoring can be used to adjust dosing schedule and to monitor compliance as well as to observe for myelotoxicity.

Maintenance anti-TNF is becoming increasingly common for those with severe disease. The REACH study suggested that children with infusions every 8 weeks were more likely to maintain remission than those treated 12 weekly [60]. While arguably not a maintenance treatment, surgery does play a role in the management of children with persistent growth deficits with or without the presence of gastrointestinal symptoms.

Summary

Nutritional impairment in children with Crohn's disease is common but is not universal. Poor nutritional state (manifest by deficits in height and weight) is most likely at diagnosis but may persist despite many years of disease treatment. Overweight and obesity can also occur.

Exclusive enteral nutrition can reduce clinical symptoms, and improve biochemical markers of inflammation. In children this treatment is as effective as steroids with more positive impacts on linear growth and mucosal healing.

Alternative treatment options include corticosteroids and other immune-suppressants; however adjuvant nutritional support is likely to be of benefit to most children.

References

1. Kelsen J, Baldassano RN. Inflammatory bowel disease: the difference between children and adults. Inflamm Bowel Dis. 2008;14 Suppl 2:S9–11.
2. Sawczenko A, Sandhu BK, Logan RF, Jenkins H, Taylor CJ, Mian S, et al. Prospective survey of childhood inflammatory bowel disease in the British Isles. Lancet. 2001;357:1093–4.
3. Sawczenko A, Sandhu BK. Presenting features of inflammatory bowel disease in Great Britain and Ireland. Arch Dis Child. 2003;88:995–1000.
4. IBD Working Group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. Inflammatory bowel disease in children and adolescents: recommendations for diagnosis—the Porto criteria. J Pediatr Gastroenterol Nutr. 2005;41:1–7.
5. Wiskin AE, Wootton SA, Beattie RM. Nutrition issues in pediatric Crohn's disease. Nutr Clin Pract. 2007;22:214–22.
6. Hildebrand H, Karlberg J, Kristiansson B. Longitudinal growth in children and adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 1994;18:165–73.
7. Kanof ME, Lake AM, Bayless TM. Decreased height velocity in children and adolescents before the diagnosis of Crohn's disease. Gastroenterology. 1988;95:1523–7.
8. Pfefferkorn M, Burke G, Griffiths A, Markowitz J, Rosh J, Mack D, et al. Growth abnormalities persist in newly diagnosed children with Crohn disease despite current treatment paradigms. J Pediatr Gastroenterol Nutr. 2009;48:168–74.
9. Vasseur F, Gower-Rousseau C, Vernier-Massouille G, Dupas JL, Merle V, Merlin B, et al. Nutritional Status and Growth in Pediatric Crohn's Disease: A Population-Based Study. Am J Gastroenterol. 2010;105:1893–900.
10. Sawczenko A, Ballinger AB, Croft NM, Sanderson IR, Savage MO. Adult height in patients with early onset of Crohn's disease. Gut. 2003;52:454–5. author reply 455.
11. Sawczenko A, Ballinger AB, Savage MO, Sanderson IR. Clinical features affecting final adult height in patients with pediatric-onset Crohn's disease. Pediatrics. 2006;118:124–9.
12. Long MD, Crandall WV, Leibowitz IH, Duffy L, Del Rosario F, Kim SC, et al. Prevalence and epidemiology of overweight and obesity in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2005;41(1):1–7.
13. Kugathasan S, Nebel J, Skelton JA, Markowitz J, Keljo D, Rosh J, et al. Body mass index in children with newly diagnosed inflammatory bowel disease: observations from two multicenter North American inception cohorts. J Pediatr. 2007;151:523–7.
14. Bechtold S, Alberer M, Arenz T, Putzker S, Filipiak-Pittroff B, Schwarz HP, et al. Reduced muscle mass and bone size in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis. 2010;16:216–25.

15. Sylvester FA, Leopold S, Lincoln M, Hyams JS, Griffiths AM, Lerer T. A two-year longitudinal study of persistent lean tissue deficits in children with Crohn's disease. Clin Gastroenterol Hepatol. 2009;7:452–5.
16. Thayu M, Shults J, Burnham JM, Zemel BS, Baldassano RN, Leonard MB. Gender differences in body composition deficits at diagnosis in children and adolescents with Crohn's disease. Inflamm Bowel Dis. 2007;13:1121–8.
17. Boot AM, Bouquet J, Krenning EP, de Muinck Keizer-Schrama SM. Bone mineral density and nutritional status in children with chronic inflammatory bowel disease. Gut. 1998;42:188–94.
18. Burnham JM, Shults J, Semeao E, Foster BJ, Zemel BS, Stallings VA, et al. Body-composition alterations consistent with cachexia in children and young adults with Crohn disease. Am J Clin Nutr. 2005;82:413–20.
19. Sentongo TA, Semeao EJ, Piccoli DA, Stallings VA, Zemel BS. Growth, body composition, and nutritional status in children and adolescents with Crohn's disease. J Pediatr Gastroenterol Nutr. 2000;31:33–40.
20. Dubner SE, Shults J, Baldassano RN, Zemel BS, Thayu M, Burnham JM, et al. Longitudinal assessment of bone density and structure in an incident cohort of children with Crohn's disease. Gastroenterology. 2009;136:123–30.
21. Wiskin AE, Wootton SA, Hunt TM, Cornelius VR, Afzal NA, Jackson AA, et al. Body composition in childhood inflammatory bowel disease. Clin Nutr. 2011;30:112–5.
22. Ahmed SF, Horrocks IA, Patterson T, Zaidi S, Ling SC, McGrogan P, et al. Bone mineral assessment by dual energy X-ray absorptiometry in children with inflammatory bowel disease: evaluation by age or bone area. J Pediatr Gastroenterol Nutr. 2004;38:276–80.
23. Filippi J, Al-Jaouni R, Wiroth JB, Hebuterne X, Schneider SM. Nutritional deficiencies in patients with Crohn's disease in remission. Inflamm Bowel Dis. 2006;12:185–91.
24. Revel-Vilk S, Tamary H, Broide E, Zoldan M, Dinari G, Zahavi I, et al. Serum transferrin receptor in children and adolescents with inflammatory bowel disease. Eur J Pediatr. 2000;159:585–9.
25. Goodhand JR, Kamperidis N, Rao A, Laskaratos F, McDermott A, Wahed M, et al. Prevalence and management of anemia in children, adolescents, and adults with inflammatory bowel disease. Inflamm Bowel Dis. 2011;17(10):2162–8.
26. Fell JM, Paintin M, Arnaud-Battandier F, Beattie RM, Hollis A, Kitching P, et al. Mucosal healing and a fall in mucosal pro-inflammatory cytokine mRNA induced by a specific oral polymeric diet in paediatric Crohn's disease. Aliment Pharmacol Ther. 2000;14:281–9.
27. Bannerjee K, Camacho-Hubner C, Babinska K, Dryhurst KM, Edwards R, Savage MO, et al. Anti-inflammatory and growth-stimulating effects precede nutritional restitution during enteral feeding in Crohn disease. J Pediatr Gastroenterol Nutr. 2004;38:270–5.
28. Guzy C, Schirbel A, Paclik D, Wiedenmann B, Dignass A, Sturm A. Enteral and parenteral nutrition distinctively modulate intestinal permeability and T cell function in vitro. Eur J Nutr. 2009;48:12–21.
29. Yamamoto T, Nakahigashi M, Umegae S, Kitagawa T, Matsumoto K. Impact of elemental diet on mucosal inflammation in patients with active Crohn's disease: cytokine production and endoscopic and histological findings. Inflamm Bowel Dis. 2005;11:580–8.
30. Leach ST, Mitchell HM, Eng WR, Zhang L, Day AS. Sustained modulation of intestinal bacteria by exclusive enteral nutrition used to treat children with Crohn's disease. Aliment Pharmacol Ther. 2008;28:724–33.
31. Axelsson C, Jarnum S. Assessment of the therapeutic value of an elemental diet in chronic inflammatory bowel disease. Scand J Gastroenterol. 1977;12:89–95.
32. O'Morain C, Segal AW, Levi AJ. Elemental diet as primary treatment of acute Crohn's disease: a controlled trial. Br Med J (Clin Res Ed). 1984;288:1859–62.
33. Beattie RM, Schiffrin EJ, Donnet-Hughes A, Huggett AC, Domizio P, MacDonald TT, et al. Polymeric nutrition as the primary therapy in children with small bowel Crohn's disease. Aliment Pharmacol Ther. 1994;8:609–15.
34. Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2007;(1):CD000542.
35. Borrelli O, Cordischi L, Cirulli M, Paganelli M, Labalestra V, Uccini S, et al. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. Clin Gastroenterol Hepatol. 2006;4:744–53.
36. Thomas AG, Taylor F, Miller V. Dietary intake and nutritional treatment in childhood Crohn's disease. J Pediatr Gastroenterol Nutr. 1993;17:75–81.
37. Sanderson IR, Udeen S, Davies PS, Savage MO, Walker-Smith JA. Remission induced by an elemental diet in small bowel Crohn's disease. Arch Dis Child. 1987;62:123–7.
38. Johnson T, Macdonald S, Hill SM, Thomas A, Murphy MS. Treatment of active Crohn's disease in children using partial enteral nutrition with liquid formula: a randomised controlled trial. Gut. 2006;55:356–61.
39. Berni Canani R, Terrin G, Borrelli O, Romano MT, Manguso F, Coruzzo A, et al. Short- and long-term therapeutic efficacy of nutritional therapy and corticosteroids in paediatric Crohn's disease. Dig Liver Dis. 2006;38:381–7.
40. Seidman E, Lohouses M, Turgeon J, Bouthillier L, Morin CL. Elemental diet versus prednisolone as initial therapy in Crohn's disease:early and long term results. Gastroenterology. 1991;100:A250.
41. Knight C, El-Matary W, Spray C, Sandhu BK. Long-term outcome of nutritional therapy in paediatric Crohn's disease. Clin Nutr. 2005;24:775–9.

42. Takagi S, Utsunomiya K, Kuriyama S, Yokoyama H, Takahashi S, Iwabuchi M, et al. Effectiveness of an 'half elemental diet' as maintenance therapy for Crohn's disease: A randomized-controlled trial. Aliment Pharmacol Ther. 2006;24:1333–40.
43. Verma S, Kirkwood B, Brown S, Giaffer MH. Oral nutritional supplementation is effective in the maintenance of remission in Crohn's disease. Dig Liver Dis. 2000;32:769–74.
44. Wilschanski M, Sherman P, Pencharz P, Davis L, Corey M, Griffiths A. Supplementary enteral nutrition maintains remission in paediatric Crohn's disease. Gut. 1996;38:543–8.
45. Verma S, Holdsworth CD, Giaffer MH. Does adjuvant nutritional support diminish steroid dependency in Crohn disease? Scand J Gastroenterol. 2001;36:383–8.
46. Tanaka T, Takahama K, Kimura T, Mizuno T, Nagasaka M, Iwata K, et al. Effect of concurrent elemental diet on infliximab treatment for Crohn's disease. J Gastroenterol Hepatol. 2006;21:1143–9.
47. Matsumoto T, Iida M, Kohgo Y, Imamura A, Kusugami K, Nakano H, et al. Therapeutic efficacy of infliximab on active Crohn's disease under nutritional therapy. Scand J Gastroenterol. 2005;40:1423–30.
48. Yamamoto T, Nakahigashi M, Umegae S, Matsumoto K. Prospective clinical trial: enteral nutrition during maintenance infliximab in Crohn's disease. J Gastroenterol. 2010;45:24–9.
49. Mullen JL, Hargrove WC, Dudrick SJ, Fitts Jr WT, Rosato EF. Ten years experience with intravenous hyperalimentation and inflammatory bowel disease. Ann Surg. 1978;187:523–9.
50. Muller JM, Keller HW, Erasmi H, Pichlmaier H. Total parenteral nutrition as the sole therapy in Crohn's disease–a prospective study. Br J Surg. 1983;70:40–3.
51. McIntyre PB, Powell-Tuck J, Wood SR, Lennard-Jones JE, Lerebours E, Hecketsweiler P, et al. Controlled trial of bowel rest in the treatment of severe acute colitis. Gut. 1986;27:481–5.
52. Afzal NA, Addai S, Fagbemi A, Murch S, Thomson M, Heuschkel R. Refeeding syndrome with enteral nutrition in children: a case report, literature review and clinical guidelines. Clin Nutr. 2002;21:515–20.
53. Stroud M. Nutrition support in Adults. London: National Institute for Clinical Excelence; 2006.
54. Day AS, Whitten KE, Lemberg DA, Clarkson C, Vitug-Sales M, Jackson R, et al. Exclusive enteral feeding as primary therapy for Crohn's disease in Australian children and adolescents: a feasible and effective approach. J Gastroenterol Hepatol. 2006;21:1609–14.
55. Sandhu BK, Fell JME, Beattie RM, Mitton SG, Wilson DC, Jenkins H on behalf of the IBD working group of BSPGHAN. Guidelines for the management of inflammatory bowel disease in children in the United Kingdom. JPGN 2010;50:S1–S13.
56. Caprilli R, Gassull MA, Escher JC, Moser G, Munkholm P, Forbes A, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. Gut. 2006;55 Suppl 1:i36–58.
57. Kundhal P, Zachos M, Holmes JL, Griffiths AM. Controlled ileal release budesonide in pediatric Crohn disease: efficacy and effect on growth. J Pediatr Gastroenterol Nutr. 2001;33:75–80.
58. Prefontaine E, Macdonald JK, Sutherland LR. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2010;(6):CD000545.
59. Alfadhli AA, McDonald JW, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. Cochrane Database Syst Rev 2005;(1):CD003459.
60. Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, Johanns J, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology. 2007;132:863–73. quiz 1165–6.
61. Lipson AB, Savage MO, Davies PS, Bassett K, Shand WS, Walker-Smith JA. Acceleration of linear growth following intestinal resection for Crohn disease. Eur J Pediatr. 1990;149:687–90.
62. Davies G, Evans CM, Shand WS, Walker-Smith JA. Surgery for Crohn's disease in childhood: influence of site of disease and operative procedure on outcome. Br J Surg. 1990;77:891–4.
63. Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's Disease. Cochrane Database Syst Rev 2005;(1):CD003715.
64. Prefontaine E, Sutherland LR, Macdonald JK, Cepoiu M. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2009;(1):CD000067.

Chapter 7
Nutritional Requirements and Support in Liver Disease

Deirdre A. Kelly, Susan Protheroe, and Sara Clarke

Key Points

- The liver's central role in energy metabolism means that children with chronic liver disease may have significant failure of growth and development in the long term.
- Insufficient dietary intake and malabsorption of fat soluble vitamins are the most important factors in the development of malnutrition in children with chronic cholestasis and are both correctable and preventable.
- The key to prevention and treatment of nutritional problems in children with liver disease is close multidisciplinary working team with clinicians, dieticians and nurses.
- Accurate nutritional assessment combined with early intervention improves both short- and long-term survival particularly after liver transplantation.

Keywords Paediatric liver disease • Liver transplantation • Malnutrition • Parenteral nutrition

Introduction

The liver has a central role in energy metabolism, nutritional homeostasis and absorption of nutrients. Severe liver disease, whether acute or chronic, leads to multiorgan failure, which can have significant effects on growth and development in the long term. Malnutrition is common in infants and children with chronic liver disease (CLD). The pathophysiology of malnutrition in liver disease is complex and multifactorial and has extensive implications. Insufficient dietary intake is probably the most important factor and is correctable (Table 7.1). It is most severe in infants with chronic cholestatic liver disease, who are particularly vulnerable to the effects of malnutrition because of their high-energy and growth requirements [1].

This chapter reviews practical points in nutrition assessment and nutritional requirements and provides a guide to the various nutritional interventions available for children with acute or CLD,

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Table 7.1 Pathophysiology of malnutrition in liver disease

Reduced calorie intake
Anorexia
Fat malabsorption
Use of bile salt resins
Portal hypertension
Unpalatable feeds
Inappropriate substrate utilisation
Abnormal nitrogen metabolism
Reduction in glycogen stores
Negative protein balance
Increased metabolic needs
Energy expenditure
Calorie requirements
Hormonal dysregulation
GH/IGF-1
Insulin resistance

and undergoing liver transplantation. A better nutritional state is associated with better survival before and after liver transplantation, so that aggressive nutritional management is an important part of the care of these children.

Protein energy malnutrition (PEM) is an inevitable consequence of CLD, particularly in the developing infant. Severe malnutrition (weight and/or height <2 standard deviations below the mean) with loss of fat stores and muscle wasting used to affect 60% of infants with liver disease [2] but modern management with early referral and diagnosis means that few children in the developed world have this problem, although this is not so for less developed countries. Both morbidity and mortality post liver transplantation are related to the degree of pre-transplant malnutrition, and thus nutritional status is an important risk factor for survival [3, 4]. Although the pathophysiology is not fully understood, there are many different mechanisms leading to malnutrition. Reduced energy intake secondary to anorexia and vomiting, fat malabsorption, disordered metabolism of carbohydrate and protein, increased energy requirements and vitamin and mineral deficiencies all contribute towards growth failure.

The clinician and dietician should work together to evaluate, manage and assess the response to treatment of nutritional deficiencies at regular intervals. Malnutrition may be underestimated by appearance alone, and the severity of the absorptive and metabolic defects may vary, so children should be assessed individually to determine both content and method of nutritional support. Modes of support will range from increased oral supplementation, enteral nutrition to parenteral nutrition (PN). Accurate nutritional assessment combined with early intervention and prevention of malnutrition is essential and may increase survival as well as improve the quality of life and outcome after liver transplantation [1, 3, 5, 6].

Reduced Energy Intake

Anorexia is common and may be due to ascites and hepatosplenomegaly, repeated hospital admissions or dietary manipulations such as fluid restriction or prescription of unpalatable feeds.

Fat Malabsorption

Fat malabsorption occurs in cholestatic liver disease, accompanied by fat-soluble vitamin and essential fatty acid (EFA) deficiencies. At least 50% of long-chain triglycerides (LCT), along with fat-soluble vitamins and the essential poly-unsaturated fatty acids (PUFA), may be malabsorbed due to reduced intraluminal bile concentration [7]. Portal hypertension, leading to congested gastric and intestinal mucosa, combined with small-bowel bacterial over-growth (in the presence of a Roux en Y 'blind' loop created in a Kasai portoenterostomy) may further exacerbate malabsorption, as may Cholestyramine (which is used to reduce pruritus) by binding bile salts. Pancreatic function is usually intact [7], except for children with Alagilles syndrome in whom pancreatic lipase may be low [7–9]. Fat malabsorption produces steatorrhoea, reduction in body fat stores leading to wasting and stunting, and fat-soluble vitamin (vitamins A, D, E and K) deficiency. EFA deficiency may lead to skin rash and hair loss [10].

Hepatic Metabolism

Carbohydrate Metabolism

The liver receives portal vein blood rich in absorbed glucose, which can be stored in the liver as glycogen or circulated to extrahepatic tissues, especially muscle, where lactate, pyruvate, and alanine are generated by glycolysis [11, 12]. In children with liver disease, this substrate supply and use can be abnormal. The loss of glycogen stores in CLD leads to fasting hypoglycemia and an inability to meet energy demands.

Protein Metabolism

Amino acids are absorbed by the intestine directly into the portal vein and transferred to the liver, where they are synthesized into protein or used for energy. The liver is responsible for approximately 10% of plasma protein synthesis; thus, amino acids are constantly recycled [12, 13]. Nonessential amino acids are oxidized in both liver and muscle. The seven aromatic essential amino acids (AAAs; arginine, histidine, lysine, methionine, phenylalanine, tryptophan and threonine) are metabolized in the liver, whereas the three branched-chain essential amino acids (BCAAs; leucine, isoleucine and valine) are metabolized predominantly in muscle and pass unaltered through the liver to the periphery, where their uptake is regulated by insulin [14]. The liver is also responsible for detoxification of nitrogenous wastes via the urea cycle, leading to the production of ammonia—hence the rise of plasma ammonia in both acute and chronic liver failure [15]. Reduced hepatic and muscle glycogen stores lead to early recruitment of fat and increased dependence on amino acids as an alternative fuel [16]. Abnormal protein use by the liver leads to a rise in AAAs and a reduction in the BCAAs, which are metabolized in muscle in both children and adults [17–19].

A study of protein metabolism in infants with liver disease, which used a whole-body leucine turnover model, demonstrated that muscle protein degradation and protein oxidation were increased, possibly as a result of a reduction in carbohydrate metabolism and the use of protein as an energy supply [20]. In contrast to normal children, muscle protein degradation continued in these children even when they were fed, suggesting that this could be a factor in the muscle loss common in infants with CLD. A recent study in cholestatic children also documented increased leucine oxidation in the postabsorptive state, but not in the fed state, but these children had less severe liver disease than the above study [21].

These metabolic changes result in muscle wasting, hyperammonaemia, hypoproteinaemia, hypoglycaemia, hyperlipaemia and reduced circulating triglycerides (due to increased fat oxidation).

Fat Metabolism

Most dietary fat is in the form of long-chain triglyceride (LCT) and is an excellent energy source [22]. The first step in fat digestion is emulsification in the stomach, followed by hydrolysis of triglyceride by pancreatic lipase in the intestinal lumen and then micellar solubilisation of di- and monoglycerides by bile acids which are then transported into the enterocytes. Once in the enterocyte, fatty acids are re-esterified and chylomicrons are formed and removed via the lymphatics through the portal system to the liver and other tissues [22].

In contrast, medium-chain triglyceride (MCT) does not depend on micellar solubilisation for absorption and can be transferred directly from the enterocyte to the portal circulation without re-esterification [23]. In the liver, free fatty acids are metabolized into triglycerides or oxidized for energy. The lipoproteins very low density lipoprotein (VLDL) and high density lipoprotein (HDL) are synthesized in the liver as is cholesterol which is the precursor for many hormones, vitamins and bile acids.

In all forms of CLD there is reduction in the synthesis and secretion of bile salts, although this is more severe in cholestatic diseases such as biliary atresia. Up to 50% of long-chain triglyceride (LCT), fat soluble vitamins and essential polyunsaturated fatty acids (PUFA) may not be absorbed because of reduced biliary secretion and reduction in intraluminal bile concentration [24]. In contrast, 95% of water soluble lipids, such as MCT, which does not depend on bile solubility, are absorbed even in cholestatic infants [6], and form the basis for nutritional replacement [25].

Long-Chain Polyunsaturated Fatty Acids

Long-chain polyunsaturated fatty acids (LCP or PUFA) such as arachidonic acid (AA) and docosahexaenoic acid (DHA) are essential nutrients in infancy. LCP, in particular DHA, plays a major role in the development of visual acuity and mental development in the first year of life, particularly in pre-term infants [26, 27]. The main source of LCP is maternal, in the last trimester of pregnancy, and through breast feeding as breast milk is a rich source of LCP containing both arachidonic acid and DHA in the combination of phospholipid and triglyceride forms.

Children with cholestatic liver disease have normal LCP and DHA levels at birth but may become deficient within 8–12 weeks [28] either from malabsorption of LCT or prescription of formula feeds rich in MCT.

Fat Soluble Vitamin Deficiency

CLD affects vitamin absorption, metabolism and storage. Reduction in bile salt secretion leads to malabsorption of the fat soluble vitamins A, D, E and K. Fat soluble vitamin deficiency may develop within 6–12 weeks of birth dependent on body stores and availability of vitamin supplementation. Vitamin A deficiency may also develop secondary to reduction in protein synthesis or depletion of hepatic stores. Vitamin D deficiency may either occur from fat malabsorption or reduction in hepatic 25 hydroxylation. Vitamin K deficiency arises partly from fat malabsorption, and partly from a reduction in intake particularly in breast fed infants [25].

As the liver has a central role in lipoprotein metabolism and cholesterol synthesis, hypercholesterolemia and hypertriglyceridaemia are common in CLD. There may be increased synthesis of cholesterol esters due to loss of hepatic lecithin cholesterol acyl transferase (LCAT) which may alter lipoprotein fractions. In cholestatic liver disease such as Alagilles syndrome cutaneous xanthomata may occur [9].

Growth Hormone/Insulin-Like Growth Factor Axis

Growth failure in CLD may be exacerbated by an impaired growth hormone (GH)/insulin-like growth factor (IGF-1) axis [29, 30], as IGF-1 and its major circulating binding protein IGF-BP3 are synthesized in the liver. Children with CLD have low plasma levels of IGF-1 despite elevated growth hormone, which may be due to diminished hepatic synthesis, malnutrition or related to end organ insensitivity to IGF-1 [30–32].

Increased Energy Expenditure

Small studies have indicated an increase in energy requirements up to 140% in children with CLD [33, 34]. Mechanisms implicated include porto-systemic shunting and ascites, abnormal intermediate metabolism and the energy demands of specific complications such as sepsis and variceal haemorrhage. Children with acute liver failure also have excess energy expenditure and requirements because of multiorgan failure, but this has not been specifically studied.

Consequences of Malnutrition

Many different nutrient deficiencies occur in children with CLD (Table 7.2) while malnutrition may increase liver dysfunction because of the energy required for synthesis, storage and detoxification. Children with progressive cholestasis such as those with biliary atresia or Alagilles syndrome develop significant fat malabsorption, which leads to steatorrhoea, fat soluble vitamin deficiency, EFA deficiency, loss of fat stores and a reduction in growth (Tables 7.2 and 7.3). EFA deficiency may present with a skin rash while DHA deficiency is associated with abnormalities in visual function as demonstrated by electroretinograms in cholestatic infants [28]. Fat soluble vitamin deficiency is more common, and can be detected biochemically before clinical symptoms which are only obvious with severe deficiencies. Clinical signs and symptoms of vitamin A deficiency are rare but include night blindness, xerophthalmia and keratomalacia [5]. Vitamin D deficiency leads to hypocalcaemia, hypophosphataemia, rickets and pathological fractures, particularly in infants who are rarely exposed to sunlight or who have inherited metabolic liver disease and a renal tubular disorder. Deficiency of vitamin E leads to haemolysis,

Table 7.2 Clinical manifestations of malnutrition in liver disease

Aetiology	Clinical manifestations
Protein energy malnutrition	Growth failure
Protein catabolism	Muscle wasting, motor development delay
Fat malabsorption	Steatorrhoea
EFA deficiency	Peeling skin rash
Vitamin A deficiency function, night blindness	Conjunctival and corneal drying, abnormal retina
Vitamin E deficiency haemolysis	Peripheral neuropathy, ophthalmoplegia, ataxia,
Vitamin D deficiency	Osteopenia, rickets, fractures
Vitamin K deficiency	Bruising, epistaxis, coagulopathy
Zinc deficiency	Acrodermatitis, anorexia, poor growth
Hypercholesterolaemia	Xanthomata
Impaired gastrointestinal function, hypochlorhydria, reduced mucosal function	Diarrhoea
Immunosuppression secondary to reduced cell-mediated immunity	Systemic infections

Table 7.3 Feeds used in paediatric liver disease

Feed	Protein source	Protein g/100 mL	kcal/100 mL/s	CHO g/100 mL	Fat g/100 mL/s	Na mmol/100 mL
Peptijunior Cow and Gate	Hydrolysed Whey	1.8	67	6.9	3.6 50% LCT:50% MCT	0.9
Pregestimil Mead Johnson	Hydrolysed Casein	1.9	68	6.9	3.8 45% LCT:55% MCT	1.3
Caprilon SHS International	Whey protein	1.5	66	7.0	3.6 25% LCT:75% MCT	0.9
Generaid Plus SHS International	Whey protein + BCAA	2.4	102	13.6	4.2 68% LCT:32% MCT	0.7
Heparon Junior SHS International	Whey protein	2	86.4	11.6	3.6 51% LCT:49% MCT	0.7
Modular Feed	Whey powder	0-flexible	70–200	7–25	Flexible 50–65%LCT:50–65%MCT	0–1.5 mmol/kg

peripheral neuropathy and occasionally visual loss [5]. Vitamin K deficiency may present as haemorrhagic disease of the newborn particularly in breast fed babies who are given insufficient vitamin K at birth [35]. It leads to coagulopathy, which is exacerbated by decreased synthesis of liver-dependent clotting factors. In vitamin K deficiency secondary to fat malabsorption, parenteral vitamin K will improve the coagulation profile whereas it will be ineffective in parenchymal liver disease [35].

Metabolic bone disease with reduced bone density is usually observed in end stage liver disease [36]. Although malabsorption of vitamin D is a factor, the aetiology is more complex as normal levels of vitamin D do not prevent bone de-mineralisation [36]. Trace element and mineral deficiencies include iron deficiency with anaemia, zinc deficiency which leads to acrodermatitis, immunodeficiency and altered protein metabolism, while both zinc and selenium deficiency may exacerbate growth failure and poor protein synthesis [1].

In the course of chronic liver failure, fat malnutrition develops first as demonstrated by loss of fat stores. Protein malnutrition is a late development and is associated with a reduction in muscle bulk, stunting and significant motor developmental delay. In time, children with significant malnutrition will have impaired growth and psychosocial development [37].

Practice and Procedures

Assessment of Malnutrition

Assessment and monitoring of patients involves clinical assessment (Table 7.1) and anthropometric, laboratory and radiological tests.

Anthropometry

Growth failure may precede the clinical signs of liver disease such as ascites or splenomegaly. Measurements of body weight and linear growth detect acute malnutrition (decreased weight for height) and chronic malnutrition (decreased height for age) [38]. The ratio between head circumference and mid-arm circumference (MAC) indicates malnutrition in children under the age of 5 (normal >0.3). Anthropometry, especially, triceps skin fold (TSF) and MAC are useful indicators of body fat and protein reserves and allow the calculation of mid-arm muscle area, which reflects body muscle mass. Serial anthropometric recording—Ii TSF may demonstrate early loss of fat stores before weight and height changes become obvious [39].

For comparison, data is expressed as standard deviation scores (or *'Z'* scores) related to the median value for the child's age and sex, where a Z score of 0 equals the 50 percentile.

Practical Difficulties when Monitoring Infants with Liver Disease

The need for nutritional support in infants with liver disease is often underestimated due to abnormal body composition. Body weight is a useful index of nutrition in most children, but is unreliable in patients with liver disease with ascites and/or organomegaly. Linear growth may be more sensitive but is a late sign growth failure in infancy, particularly as stunting (or negative height velocity) may not be apparent until 1 year of age [25]. Serial measurements of MAC and TSF, taken in combination with changing trends in height or weight, are the most sensitive indicators for the instigation of nutritional support.

Selecting Patients for Nutritional Support

Patients at Particular Risk of Development of Malnutrition

Under 2 years of age; Severe cholestasis (serum bilirubin >70 mmol/L; >50% conjugated); Progressive liver disease such as biliary atresia, severe neonatal hepatitis; Patients awaiting liver transplantation.

Growth failure should be anticipated and prevented by frequent anthropometric assessment. Urgent support is required if the MAC and TSF are more than two standard deviations below the mean.

Nutritional Requirements and Strategies for Nutritional Support

Nutritional intervention should attempt to compensate for anorexia, increased energy requirements, malabsorption and abnormal hepatic metabolism. It is recommended all units managing cholestatic infants as a nutrition protocol [40]. Nutritional rehabilitation is catered to the individual child but generally the caloric intake is increased to at least 130% of recommended daily allowance (RDA).

Components of Nutritional Support

Lipids

The energy value of dietary lipids is 8–9 kcal/g. They are the major energy source for infants. Increasing fat intake to provide 30–50% of total energy intake [25], despite increasing steatorrhoea, may increase the overall amount of fat absorbed [7].

Medium-Chain Triglycerides

Medium-chain triglycerides (MCT) are well absorbed in cholestatic infants. Therefore, the addition of 30–50% MCT is a useful substrate, reducing steatorrhoea [6] with subsequent nutritional improvement [7, 25]. Nutritionally complete MCT containing infant formula designed specifically for use in cholestatic liver disease are available (Table 7.3).

Essential Fatty Acids

Although the exact requirements for infants are not known, clinical deficiency symptoms may occur at PUFA intakes below 1% of energy. Mature human milk contains 11% wt/wt EFAs. The minimal intake of linoleic acid recommended for young infants is 2.7–4.5% of energy and a ratio of linoleic:linolenic acid of 5:1 [27].

Fat-Soluble Vitamins

Fat-soluble vitamins are supplemented in large quantities especially in children with cholestasis along with other vitamins and minerals. In order to optimize absorption, it is best to prescribe these vitamins separately [6, 25]. Generous oral doses may be required to produce therapeutic plasma concentrations. Occasionally, intramuscular vitamin D is required.

Carbohydrate

Complex carbohydrates such as maltodextrin or glucose polymer (Maxijul, SHS International) restrict the osmolality of the feed while maintaining a high energy density allowing fluid restriction. Additions are made slowly on a daily basis to establish intestinal tolerance.

Protein

There may be a reluctance to increase protein intake beyond the estimated requirement for normal children because low protein diets were previously prescribed to prevent encephalopathy. Increasing the calorie density of proprietary infant formulae with carbohydrate and fat supplements alone reduces the percentage energy from protein. Concentrating infant formula enhances intake whilst maintaining the balance between energy and protein in feeds. It is now recognized that infants with advanced liver disease may tolerate up to 4 g/kg/day protein without encephalopathy or all increase ill plasma amino acid abnormalities [6, 25].In practice, 3–4 g/kg/day of a whole protein, which is more palatable, is preferred.

Mineral Supplementation

Zinc deficiency secondary to chronic malabsorption may contribute to anorexia and poor linear growth. Plasma zinc concentration may not reflect total body zinc status, but supplementation may be helpful if deficiency is suspected because of persistent poor growth.

Feed Choices

Cholestatic infants in the early stages of disease will compensate for the degree of malabsorption by increasing their intake, often consuming 120–200% more formula than the recommended intake for age. To improve nutrient absorption an infant formula rich in MCT infant formula (Table 7.3) should replace normal infant formula for bottle fed infants or be used as a supplement alongside breast milk in the breast fed infant.

For infants with continued poor growth and subsequent reduced feed intakes MCT formula can be concentrated from 13% standard dilution to 15–19% dilution. This increases energy density from 67 kcal/100 mL to 80–100 kcal/100 mL and protein from 1.9 g/100 mL to 2.24–2.84 g protein/100 mL. Concentrating formula feeds increases intake of all nutrients and maintains the delicate balance

between energy, protein and micronutrients. The practice of concentrating infant formula should only be undertaken by an experienced paediatric dietician who can ensure the infant continues to receive appropriate total nutrition.

If ascites or encephalopathy develop, fluid and salt restriction may make commercial feeds impractical and a modular feeding system may be of benefit. The modular feeding system is extremely flexible in its composition and can be manipulated easily to suit the child's specific nutritional requirements.

The individual prescription of protein, energy, sodium and water produces a patient specific feed of high-energy density (1–2 kcal/mL) with restricted sodium, fluid or protein as appropriate. Calogen (Nutricia Advanced Medical Nutrition) and Liquigen (SHS International) emulsions supply LCT and MCT. Protifar, a whey protein powder (Nutricia Advanced Medical Nutrition), and Maxijul (SHS International), a complex carbohydrate polymer, provide protein and carbohydrate components respectively. Vitamin and mineral requirements are added (e.g. Paediatric Seravit, SHS International) as well as sodium (not <1 mmol/kg/day for growth) and potassium (as molar solutions).

Mode of Delivery

Enteral Feeds

Early enteral tube feeding should be considered for infants and children with CLD [25, 37]. A soft silastic nasogastric tube is well accepted in infants. It is not, by itself, likely to provoke bleeding from oesophageal varices, and it allows reliable delivery of nutrition support and medications. It is essential to prepare infants with play therapy and to train parents carefully. The success of home enteral feeding depends on a dedicated multi-disciplinary team including dietician, specialist nurses, clinician and community support. Intensive enteral feeding is highly effective in reversing malnutrition infants with liver disease. It can relieve parenteral anxiety regarding oral intake and may induce a transformation in the child's affect and even increase voluntary intake [25].

Behavioural Feeding Problems

Behavioural feeding problems are common secondary to long-term tube feeding, unpalatable feeds or medications. These infants may miss their developmental milestones for chewing, swallowing and perhaps speech. The pre-transplant emphasis intensive nutritional support often creates parental anxiety about feeding. It is not surprising that behavioural feeding problems may become manifest pre- and post-transplantation and contribute to persistent growth failure. Strategies to prevent this include encouraging daytime feeding to provide oral stimulation particularly if nocturnal nasogastric feeding is undertaken. A multi-disciplinary approach, involving the participation of clinician, dietician, nurse specialist, clinician psychologist and play therapist is required to treat these difficult problems [40].

Post Liver Transplantation

Parenteral nutrition (PN) is commenced on post-operative day 1 for infants with pre-transplant malnutrition, only if feeding is to be delayed. In most cases, enteral feeding is started as soon as post-operative ileus has resolved. Nutritional support provides an energy intake of around 120% of EAR as a high energy paediatric enteral feed, a high energy infant formula or a modular feed prior to discharge. Additional supplements of fat and carbohydrate may be required for some time to maintain

growth while establishing normal oral intake. In 10% of children, nocturnal enteral feeding is required for up to 1–2 years; osteopenia often persists after successful liver transplantation (LT), and it may take many months of vitamin D and adequate nutrition to correct [36, 37].

Parenteral Nutrition

Parenteral nutrition (PN) is rarely necessary in CLD; however, if there is severe PEM, feed intolerance and malabsorption, PN, in combination with enteral nutrition, improves nutrient delivery. Short-term PN is essential during complications such as intra-abdominal sepsis, variceal bleeding and liver failure, which are associated with marked catabolism and weight loss. Nutrition should aim to blunt this catabolic state and enhance anabolic activity during recovery while avoiding overfeeding. Despite perceived reluctance to use PN in children with CLD because of the association with hepato-biliary dysfunction, short-term PN is a life-saving therapy and does not invariably increase cholestasis.

Standard amino acid mixtures (e.g. Vaminolact) are generally safe and lipids provide a key source of calories, correcting energy deficits. When parenteral lipid emulsions are given in excess of the liver's ability to process them, hyperlipidaemia and hepatic steatosis may occur [41]. Lipids are generally administered to provide 30% of total calories, but should be used with caution and dosage reduction considered when impaired hepatic clearance is present, especially if sepsis is present, to avoid further rises in triglyceride concentrations [41]. Soybean lipid emulsions contain phytosterols, which may be associated with cholestasis [41] and the oil source of the emulsion may also affect the relative risk of developing abnormal liver function, known as intestinal failure-associated liver disease (IFALD) [42].

Evidence suggests also that soybean-based lipid emulsions (e.g. Intralipid) with high contents of PUFA are a causative factor in IFALD since these lipids are rich in ω-6 fatty acids, which are pro-inflammatory and may act to promote hepatocyte damage and lipid peroxidation, which can exacerbate oxidative stress [43]. More recently developed parenteral lipid emulsions substitute soybean oil with a variety of oils providing MCT, ω-9 monounsaturated fatty acids or ω-3 PUFA or fish oil lip emulsions. The mixed lipid emulsions (e.g. SMOF) have demonstrated reduced effects on oxidative stress, immune responses and inflammation, while the fish oil lipid emulsions may be beneficial in improving IFALD [43–45]. However, the effects of these new lipid emulsions on clinical outcomes have not been extensively evaluated [43].

Septic events also play a key role in the development of IFALD. Careful line care, reduction in maximal lipid dose or alternate lipids such as ω-3 fatty acids should be adopted to prevent liver damage [44]. Patients on partial PN need careful biochemical monitoring and attention to fluid and electrolyte balance, including concurrent intravenous infusion therapy to avoid fluid overload.

Delivery of PN

Central venous catheterization with double or triple lumen catheter offers convenient and reliable venous access if the duration of feeding is more than a week [46].

Laboratory Parameters

Serial monitoring of laboratory parameters may detect malnutrition in time to allow nutritional intervention. Proteins, such as albumin or retinol-binding protein, may assess recent or long-term adequacy of protein and calorie intake, but are non-specific as serum protein concentrations may vary due to protein loss, distribution, vitamin and mineral status and hepatic disease.

Laboratory monitoring of calcium, phosphate and magnesium levels reflects. Plasma concentrations of vitamins A and E demonstrate therapeutic levels and stores. Coagulation tests reflect both hepatic synthetic function and vitamin K supplementation. Zinc may be depleted in patients with persistent anorexia or poor growth. Measurement of triglyceride and cholesterol may assess the balance of the energy providing fuels in the feed, while plasma amino acids may assess protein metabolism in the face of progressive liver dysfunction.

Radiology

Wrist and knee X-rays are performed to detect osteopenia and rickets if alkaline phosphatase is elevated (>1,000 IU).

Conclusion

An understanding of the pathophysiological mechanisms contributing towards malnutrition in infants with liver disease is essential when planning therapeutic strategies. Growth failure should be anticipated by serial anthropometric assessment. This includes the estimation of fat and muscle stores by measurement of MAC and TSF as estimates of body composition. Patients at particular risk of development of malnutrition are those with severe cholestasis, progressive liver disease and those awaiting liver transplantation.

The first step in nutritional support for infants with liver disease includes increased calorie intake, generous oral fat soluble vitamin supplementation and nasogastric tube feeding. It is vital to increase the energy intake to 130–180% of EAR [25, 40]. This is achieved by introducing MCT containing infant formula, concentrating infant formula or supplementing feeds with extra fat and carbohydrate to produce a feed with a high-energy density (>1 kcal/mL) and with an intake of 3–4 g/kg/day protein. Nocturnal enteral feeding may circumvent the abnormal homeostatic control of carbohydrate and protein metabolism and avoid vomiting due to the small capacity of the stomach. A modular feed system permits flexibility in infants with end-stage liver disease when fluid or salt restriction for management of ascites may make commercially available nutritionally complete feeds impractical.

Nourishing children with liver disease is a challenging task; however, appropriate assessment and well-timed nutritional interventions are paramount for a good long-term outcome in these patients. An appropriate balance of macronutrients, micronutrients and vitamins is important, as is the route of administration. Key to providing successful nutritional support is involvement of a multi-disciplinary team including paediatric dietician, liaison nurse, feeding psychologist and clinician.

References

1. Chin SE, Shepherd RW, Thomas BJ, Cleghorn GJ, Patrick MK, Wilcox JA, et al. The nature of malnutrition in children with end stage liver disease. Am J Clin Nutr. 1992;56:164–8.
2. Beath S, Pearmain G, Kelly D, McMaster P, Mayer D, Buckels J. Liver transplantation in babies and children with extrahepatic biliary atresia. J Pediatr Surg. 1993;28(8):1044–7.
3. Moukarzel AA, Najm I, Vargas J, McDiarmid SV, Busutti RW, Ament ME. Effect of nutritional status on outcome of orthotopic liver transplantation in pediatric patients. Transplant Proc. 1990;22:1560–3.
4. Beath S, Brook G, Kelly D, McMaster P, Mayer D, Buckels J. Improving outcome of liver transplantation in babies less than 1 year. Transplant Proc. 1994;26:180–1.
5. Chin SE, Shepherd RW, Thomas BJ, Cleghorn GJ, Patrick MK, Wilcox JA, et al. Nutritional support in children with end-stage liver disease: a randomized crossover trial of a branched-chain amino acid supplement. Am J Clin Nutr. 1992;56(1):158–63.

6. Nightingale S, Ng VL. Optimizing nutritional management in children with chronic liver disease. Pediatr Clin North Am. 2009;56(5):1161–83.
7. Beath S, Hooley I, Willis K, Johnson S, Kelly D, Booth I. Long chain triacyglycerol malabsorption. Clin Endocrinol. 1993;52:252A.
8. Chong SK, Lindridge J, Moniz C, Mowat AP. Exocrine pancreatic insufficiency in syndromic paucity of interlobular bile ducts. J Pediatr Gastroenterol Nutr. 1989;9(4):445–9.
9. Kamath BM, Loomes KM, Piccoli DA. Medical management of Alagille's syndrome. J Pediatr Gastro Nutr. 2010;50(6):580–6.
10. Pawłowska J, Socha P, Socha J. Nutrition in pediatric patients before liver transplantation. Rocz Panstw Zakl Hig. 2007;58(1):111–8.
11. Romijn JA, Endert E, Sauerwein HP. Glucose and fat metabolism during short-term starvation in cirrhosis. Gastroenterology. 1991;100:731–7.
12. Boyer Td, Manns MP, Sanyal AJ, Hellerston MM. Interaction of liver, muscle and adipose tissue in the regulation of metabolism in response to nutritional and other factors. In: The liver: biology and pathobiology. 3rd ed. New York: Raven; 1994. p. 1169–91.
13. Yudkoff M, Nissim I, McNellis W, Polin R. Albumin synthesis in premature infants: determination of turnover with [15N]glycine. Pediatr Res. 1987;21:49–53.
14. Duggan C, Watkins JB, Walker A, Miller L. The role of the liver and the non-hepatic tissues in the regulation of free amino acid levels in the blood. In: Amino acid pools A. Amsterdam: Elsevier; 1962. p. 708–9.
15. Powers Lee SG, Meister L. Urea synthesis and ammonia metabolism. In: Arias M, Jakoby WB, Popper H, Schalter D, Shafritz DA, editors. The liver: biology and pathobiology. New York: Raven; 1988. p. 317–30.
16. McCullough AJ, Mullen KD, Smanik EJ, Tabbaa M, Szauter K. Nutritional therapy and liver disease. Gastroenterol Clin North Am. 1989;18:619–43.
17. Weisdorf SA, Freese DK, Fath JJ, Tsai MY, Cerra FB. Amino acid abnormalities in infants with extrahepatic biliary atresia and cirrhosis. Pediatr Gastroenterol Nutr. 1987;6:860–4.
18. Kawaguchi T, Izumi N, Charlton MR, Sata M. Branched-chain amino acids as pharmacological nutrients in chronic liver disease. Hepatology. 2011;54(3):1063–70.
19. Ramaccioni V, Soriano HE, Arumugam R, Klish WJ. Nutritional aspects of chronic liver disease and liver transplantation in children. J Pediatr Gastroenterol Nutr. 2000;30(4):361–7.
20. Protheroe S, Jones R, Kelly DA. Evaluation of the role of branched chain amino acids in the treatment of protein malnutrition in infants with liver disease. Gut. 1995;37:A30.
21. Mager DR, Wykes LJ, Roberts EA, Ball RO, Pencharz PB. Mild-to-moderate chronic cholestatic liver disease increases leucine oxidation in children. J Nutr. 2006;136(4):965–70.
22. Duggan C, Watkins JB, Walker A, Dyke RV. Mechanisms of digestion and absorption of food. In: Gastrointestinal disease, pathophysiology, diagnosis, management. 4th ed. Philadelphia: WB Saunders; 1989. p. 1062–1088.
23. Carey M, Small DM, Bliss CM. Lipid digestion and absorption. Annu Rev Physiol. 1983;45:651–77.
24. Phan CT, Tso P. Intestinal lipid absorption and transport. Front Biosci. 2001;6:D299–319.
25. Beath SV, Booth IW, Kelly DA. Nutritional support in liver disease. Arch Dis Child. 1993;69:545–9.
26. Makrides M, Neumann M, Simmer K, Pater J, Gibson R. Are long-chain polyunsaturated fatty acids essential nutrients in infancy? Lancet. 1995;345:1463–8.
27. Koletzko B, Agostoni C, Carlson SE, Clandinin T, Hornstra G, Neuringer M, et al. Long chain polyunsaturated fatty acids (LC-PUFA) and perinatal development. Acta Paediatr. 2001;90:460–4.
28. Spray CH, Beath S, Willis KD, et al. Docosahexaenoic acid (DHA) and visual function in infants with fat malabsorption secondary to liver disease. Proceed Nutr. 1995;54:108A.
29. Holt RI, Jones JS, Stone NM, Baker AJ, Miell JP. Sequential changes in insulin-like growth factor I (IGF-I) and IGF-binding proteins in children with end-stage liver disease before and after successful orthotopic liver transplantation. J Clin Endocrinol Metabol. 1996;81:160–8.
30. Bucuvalas JC, Horn JA, Slusher J, Alfaro MP, Chernausek SD. Growth hormone insensitivity in children with biliary atresia. J Pediatr Gastroenterol Nutr. 1996;23:135–40.
31. Holt RI, Miell JP, Jones JS, Mieli-Vergani G, Baker AJ. Nasogastric feeding enhances nutritional status in paediatric liver disease but does not alter circulating levels of IGF-I and IGF binding proteins. Clin Endocrinol. 2000;52:217–24.
32. Quirk P, Owens P, Moyse K, Chin S, Wall C, Ballard J, et al. Insulin-like growth factors I and II are reduced in plasma from growth retarded children with chronic liver disease. Growth Regul. 1994;4:35–8.
33. Pierro A, Koletzko B, Carnielli V, Superina RA, Roberts EA, Filler RM, et al. Resting energy expenditure is increased in infants and children with extrahepatic biliary atresia. J Pediatr Surg. 1989;24:534–8.
34. Protheroe SM, McKiernan PJ, Kelly DA. Can measurement of dietary-induced thermogenesis (DIT) predict response to nutritional intervention in infants with liver disease? Clin Nutr. 1996;15:39.
35. Yanofsky RA, Jackson VG, Lilly JR, Stellin G, Klingensmith III WC, Hathaway WE. The multiple coagulopathies of biliary atresia. Am J Haematol. 1984;16(2):171–80.

36. Hogler W, Baumann U, Kelly D. Growth and bone health in chronic liver disease and following liver transplantation in children. Pediatr Endocrinol Rev. 2011;7(3):266–74.
37. van Mourik ID, Beath SV, Brook GA, Cash AJ, Mayer AD, Buckels JA, et al. Long term nutritional and Neurodevelopmental outcome of liver transplantation in infants aged less than 12 months. J Pediatr Gastroenterol Nutr. 2009;30(3):269–75.
38. Waterlow J. Note on the assessment and classification of protein-energy malnutrition in children. Lancet. 1973;2:87–9.
39. Sokol RJ, Stall C. Anthropometric evaluation of children with chronic liver disease. Am J Clin Nutr. 1990;52:203–8.
40. Baker A, Stevenson R, Dhawan A, Goncalves I, Socha P, Sokal E. Guidelines for nutritional care for infants with cholestatic liver disease before liver transplantation. Paediatr Transpl. 2007;11(8):825–34.
41. Kumpf V. Parenteral nutrition associated liver disease in adult and pediatric patients. Nutr Clin Pract. 2006;21:279–90.
42. Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in parenteral nutrition of intensive care patients: current thinking and future directions. Intensive Care Med. 2000;36:735–49.
43. Calder PC, Jensen GL, Koletzko BV, Singer P, Wanten GJ. Lipid emulsions in parenteral nutrition of intensive care patients: current thinking and future directions. Intensive Care Med. 2010;36:735–49.
44. Diamond IR, de Silva NT, Tomlinson GA, Pencharz PB, Feldman BM, Moore AM, et al. The role of parenteral lipis in the development of advanced intestinal failure-associated liver disease in infants: a multiple-variable analysis. J Parenter Enteral Nutr. 2011;35(5):596–602.
45. Meijer VE, Gura KM, Le HD, Meisel JA, Puder M. Fish oil-based lipid emulsions prevent and reverse parenteral nutrition-associate liver disease: The Boston experience. J Parenter Enteral Nutr. 2009;33(5):541–7.
46. Pittiruti M, Hamilton H, Biffi R, Macfie J, Pertkiewicz M. ESPEN guidelines on parenteral nutrition: central venous catheters (access, care, diagnosis and therapy of complications). Clin Nutr. 2009;28:365–77.

Chapter 8
Normal and Aberrant Craniofacial Development and Nutrition in Infancy

Anne O'Connell

Key Points

- The oral cavity is a unique and complex environment, containing soft tissues and teeth bathed in saliva. An intact craniofacial complex is critical for the correct function of airway, mastication, speech, and swallowing.
- Failure to establish oral feeding may result in inadequate nutrient intake and delayed oromotor development.
- Structural defects and diseases affecting the oral hard and soft tissues (infectious as well as acute and chronic systemic diseases with oral manifestations) can impact negatively on a child's ability to eat.
- The feeding practices established in infancy influence subsequent food choices and feeding patterns. These behaviors are shaped by parental behaviors, which are influenced by family, education, and cultural beliefs.
- Early childhood caries (ECC) is the currently accepted term for any carious tooth in a child under 5 years of age and is the most common infectious disease in childhood.
- Treatment of the decayed teeth, eliminating night-time bottle feeding, and reducing the frequency of snacking, combined with improved tooth cleaning helps establish a healthy dentition in children.
- Medical practitioners should always request sugar free formulations when available and instruct parents to increase oral hygiene measures following ingestion of oral medication.
- Oral health must be established during childhood as part of a child's general health and development.

Keywords Craniofacial • Dental development • Oral health • Caries • Ankyloglossia • Breastfeeding

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Introduction

The oral cavity is the usual portal for nutrition throughout life and any aberrations in its development or function may impact on the capacity of an infant to thrive. The mouth is complex and unique, it is open to the environment, forms the anterior section of the gastrointestinal system and contains tissue derived from ectoderm, mesoderm, and endoderm, including teeth, in the presence of saliva. Any interference with normal development of the face, mouth, and teeth arising in utero and infancy can lead to a wide spectrum of disorders presenting at birth or in infancy. Some malformations are evident at birth, such as cleft lip/palate, Trisomy 21, and Pierre Robin Sequence. Other issues with structure and function of components of the craniofacial complex may not be immediately apparent but can complicate feeding and nutrient intake in the infant which may manifest as failure to thrive.

Faltering growth in infancy is a marker for various medical, social, and economic problems and may be attributed to inadequate nutrition [1]. Even when craniofacial development is normal, feeding difficulties can arise in the neonatal period due to biological, developmental, or behavioral issues. Reduced efficiency in feeding often occurs when there is oral motor dysfunction, which is common in children with developmental disabilities. Feeding behaviors in infancy can be shaped by parental behaviors, which are influenced by family, education, and cultural beliefs. Sweetened foods are used as rewards globally, and can often interfere with appropriate nutritional intake. In addition, diseases affecting the oral hard and soft tissues (infectious as well as acute and chronic systemic diseases with oral manifestations) can impact negatively on a child's ability to eat and maintain healthy nutritional status. Maintenance of oral health is often given a low priority when other systemic diseases are present despite the recommendations for integrating oral health into overall health care [2].

Early childhood caries (ECC) is the most common infectious disease in childhood [2]. It is a bacterially mediated disease affecting teeth that is modified by diet [3]. Previously this condition was called baby bottle tooth decay, nursing caries, and bottle mouth because of the association of the condition with poor feeding practices. Mothers who have untreated tooth decay may harbor high titers of mutans streptococci in their saliva which can be transmitted to their child, putting them at risk for ECC. One of the risk factors for dental caries is malnutrition (both under and over nutrition). Both malnutrition and caries share other risk factors such as systemic illness, disability, low socioeconomic status as well as behavioral, cultural, and psychosocial factors. Pain and infection from decayed teeth may limit adequate oral intake and many children accessing emergency dental care report disruption with eating [4]. Extensive caries may also be a sign of malnourishment or neglect.

This chapter seeks to summarize issues in the oral cavity that may impact nutritional intake, those that arise due to aberrant development, and also those that can occur during the management of other conditions. Education of medical practitioners, parents, and caregivers will be essential to ensure that oral health is maintained while nutritionally supporting the infant.

Normal Development

Craniofacial Complex

An intact craniofacial complex is critical for the correct function of airway, mastication, speech, and swallowing. Craniofacial development begins within 4 weeks after fertilization when facial, oral, and nasal components and the tongue develop from the first branchial arch in a preprogrammed coordinated manner to form the facial structure [5]. The face develops between 24 and 38 days gestational age. The mandible, lower lip, chin, and gingiva develop from the mandibular prominences. Development of the maxillary prominences results in formation of the upper lip, cheeks, maxilla, and secondary

palate. The premaxilla contributes the philtrum of the upper lip, the incisor region of the maxilla, and the primary palate. The development of the secondary palate requires a precise sequence of events that allows the tongue to descend and the palatal shelves rise and fuse in the midline (Fig. 8.1) [5]. The embryo at 9 weeks has a well developed maxilla, mandible, palate, lips, and tongue.

Teeth

Tooth development occurs within the dental arches and is initiated at 6.5 weeks gestational age with the formation of the dental lamina, which defines the upper and lower dental arches. Development of the primary dentition occurs in utero and mineralization of the primary teeth commences at 14–16 weeks in utero (Table 8.1) [6]. The permanent teeth begin formation between 16 and 20 weeks in utero and continue to develop and calcify throughout infancy (Table 8.2) [6]. The symmetry and sequence of tooth development suggest that it is under genetic control but it can be modified by hormonal imbalances, infections, metabolic disturbances, medications, and environmental factors.

The teeth emerge to a position of function within the oral cavity through the continuous process of tooth eruption. Tooth eruption requires a coordinated program of alveolar bone resorption and development of root and periodontium. This complex process is under genetic control but various factors such as gender, socioeconomic status, body composition, and craniofacial morphology may have a role [7]. The time of emergence has been defined as the time at which any part of the crown has emerged through the gingival surface, but eruption continues as each tooth moves into occlusion and does not cease as teeth may continue to erupt to compensate for the effects of wear in the oral cavity. The timing of tooth emergence varies for each tooth type, the 20 primary teeth usually have erupted by 3 years of age.

Soft Tissue Development

By 9 weeks gestational age, the tongue has formed and the soft tissues are organized within the oral cavity. The oral cavity, pharynx, and esophagus are separate regions but are controlled by the nervous system to coordinate sucking and swallowing. The development of effective sucking and swallowing involves a highly complex set of anatomical and neurological interactions that begin in utero and continue through infancy and early childhood. The tongue is attached to the oral mucosa via a fibrous connection known as the lingual frenum (or frenulum).

Saliva

Saliva has numerous functions within the oral cavity. Drooling is a normal developmental stage for an infant and results not from an excess of saliva, but lack of control of the orafacial musculature. When drooling persists, it can indicate oromotor dysfunction which may interfere with adequate nutrient intake. Salivary gland agenesis can occur, although it is rare. Saliva can also be reduced secondary to other diseases such as ectodermal dysplasia. In addition, pediatric medications for the treatment of chronic diseases can also cause salivary gland hypofunction. When saliva is reduced, there may be difficulty in forming a food bolus or in swallowing food, which may also interfere with food choice and increase the risk for nutritional imbalance and dental infection. Food choices may be restricted due to lack of saliva or frequent fluid intake may be encouraged to substitute for saliva. Professional

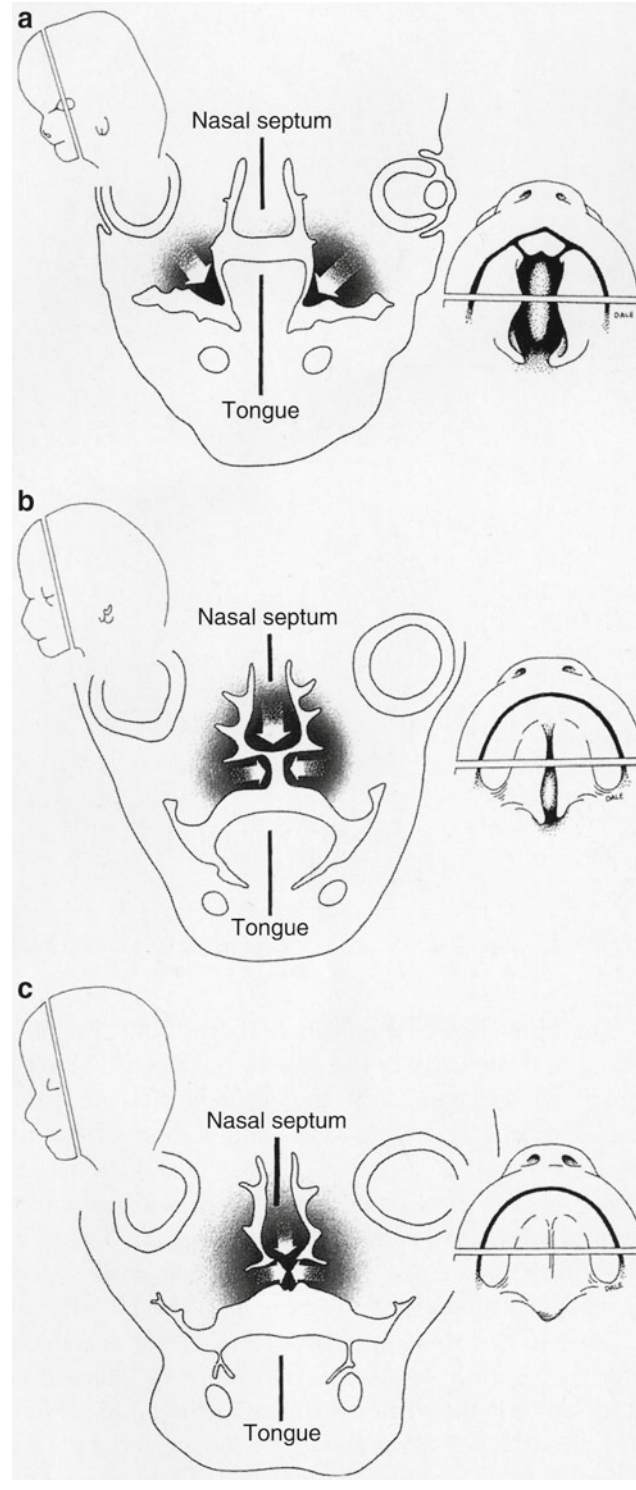

Fig. 8.1 Formation of oral structures from weeks 7 to 10 in utero. (**a**) At 7 weeks the palatal shelves are forming from the maxillary processes and lie on either side of tongue. (**b**) The tongue is depressed allowing the palatal shelves to elevate. (**c**) The shelves fuse and the nasal septum is completed (drawing reproduced with permission from ten Cate Oral Histology [5])

Table 8.1 Chronology of the human dentition (reproduced with permission, [6])

Primary teeth	Hard tissue formation begins (weeks in utero)	Amount of enamel formed at birth	Age at which enamel is completed (months after birth)	Mean age of tooth eruption (months+1 SD)
Maxillary				
Central incisor	14	Five sixths	1.5	7.5
Lateral incisor	16	Two thirds	2.5	9
Canine	17	One third	9	18
First molar	15.5	Cusps united	6	14
Second molar	19	Cusps united	11	24
Mandibular				
Central incisor	14	Three fifths	2.5	6
Lateral incisor	16	Three fifths	3	7
Canine	17	One third	9	16
First molar	15.5	Cusps united	5.5	12
Second molar	18	Cusp united	10	20

Table 8.2 Development of permanent teeth in childhood [6]

Permanent teeth	Mineralization begins (postnatal)	Enamel completed (years)
Central incisor	3–4 months	4–5
Lateral incisor	Max 10–12months	4–5
	Mand 3–4 months	4–5
Canine	4–5 months	6–7
First premolar	Max 1.75–2 years	5–6
	Mand 1.5–1.75 years	
Second premolar	2.2–2.5 years	6–7
First Molar	At birth	2.5–3
Second molar	2.5–3 years	7–8

Table 8.3 Abnormal development of oral structures that may complicate oral feeding in infancy

Anomaly	Condition
Cleft lip (palate)	Pierre Robin Sequence, Apert syndrome, Oro-facial-digital syndrome
Micrognathia	Pierre Robin Sequence, Cri du Chat, Treacher Collins, Trisomy21
Hypodontia	Ectodermal dysplasias, Riegers Syndrome, SSCI
Macrostomia	Treacher Collins, Klinfelters
Microstomia	Trisomy 17/18, Oropalataldigital syndrome
Macroglossia	Trisomy 21, Crouzon syndrome, CHARGE syndrome, Beckwith–Wiedeman, Maroteaux–Lamy syndrome, Congenital hypothyroidism
Hemifacial microsomia	Goldenhar, Turner, Hallermann–Streiff syndrome
Salivary gland hypofunction	Ectodermal dysplasia, cystic fibrosis
Delayed eruption	Cleidocranial dysplasia Ellis van Creveld, Trisomy 21, Gardner syndrome
Abnormal frenae	Oro-facial-digital syndrome,
Oral ulceration	Epidermolysis bullosa, Bechet syndrome

management by a pediatric dentist is recommended to protect oral health while supporting the medical management of the underlying condition.

Failure of craniofacial components to merge or fuse in a normal pattern can result from genetically determined events or environmental or metabolic influences. The range of craniofacial anomalies is huge and may impact on the child's ability to achieve appropriate nutrition (Table 8.3). Presence or

absence of teeth, as well as their shape, size, and location may influence nutrition for the infant. Diseases that affect hair, skin, and nails, such as the ectodermal dysplasias, feature absent or abnormal teeth and may include salivary gland hypofunction. Abnormalities associated with hard and soft tissues within the oral cavity can limit food intake and affect feeding in infants.

Intrauterine Growth Disturbances

Many factors are implicated in impaired intrauterine growth disturbances, e.g. infections, medications, and maternal smoking, which potentially can give rise to aberrant intrauterine development of the structures of the craniofacial complex and subsequent oromotor dysfunction. Major anomalies of craniofacial structures can occur due to syndromes of the first branchial arch. It is still unknown how nutritional deficiencies in the mother are related to the alteration of growth patterns in the infant. It is documented that exposure to alcohol or anticonvulsant medication in early pregnancy can result in craniofacial malformations [8].

Cleft lip and Palate

Cleft lip and palate (CL(P)) is a congenital anomaly that occurs in 0.9–1.9% live births [9]. The etiology is complex, but there is evidence for the association of specific nutrients such as folate, thiamim, niacin, zinc, magnesium, and vitamin A with clefting [10]. Defects in the musculoskeletal, central nervous system, or cardiovascular system are often associated with CL(P) when presenting as part of a syndrome e.g. DiGeorge/chromosome 22q11, Crouzon, Treacher Collins, Van der Woude, Orofacial-digital syndromes (Table 8.3). The disruption of the physical structure will affect the ability of the child to feed, and breastfeeding may not be possible. The presence of a submucous cleft should be investigated as this anatomical abnormality may not be initially obvious on the infant examination. Identification of clefting usually occurs in neonatal units where feeding support is available using special bottle teats to achieve an oral seal. A recent systematic review reported that there was no difference in growth outcomes between rigid or squeezable bottles. There was no evidence that use of palatal feeding plates improve growth in infants with clefts [11]. Early identification, surgical management, and frequent follow up by interdisciplinary teams usually prevents inadequate nutrition in the child with CL(P) [12].

Fetal Alcohol Spectrum Disorders

Prenatal exposure to alcohol causes a range of abnormalities called fetal alcohol spectrum disorders. Alcohol effects the developing craniofacial complex giving rise to a characteristic facies, including short palpebral fissures, a smooth philtrum, and a thin upper lip. Brain development is also disrupted, resulting in cognitive and behavioral problems in the infant [13]. There is a significant association between the measurement of facial features and the extent of brain dysfunction in individuals with prenatal alcohol exposure [14]. These neuropsychological deficits may present problems with feeding and appropriate weight gain in infancy [15].

Intrauterine Growth Retardation/Prematurity/Low Birthweight

Worldwide it is estimated that 8–20% of infants are born with low birth weight (LBW). These children may have been born prematurely or be small for gestational age and are at increased risk of health problems during adult life, such as cardiovascular diseases and metabolic syndrome. Metabolic syndrome is defined as the coexistence of hypertension, dyslipidemia, insulin resistance, and obesity and is thought to result from an inadequate supply of nutrients or oxygen in utero or immediately after birth.

The aim of nutritional management in infants born small is to achieve a postnatal growth rate equivalent to that of the third trimester of intrauterine life. The delivery of oral nutrition may be complicated by malabsorption, cholestasis, or enterocolitis and hypoxic brain injury may affect efficient oromotor function for ingestion of foods. Infants aged 35–36 gestational weeks are mature enough to suck and swallow milk. Less mature infants will need to be fed with breast milk supplemented with proteins, calories, and minerals through an oro- or nasogastric tube. Many studies have indicated that there are early and late effects of prematurity on the physical and psychological growth and development of these children. Failure to establish oral feeding may result in inadequate nutrient intake and delayed oromotor development. If nutrition management is unbalanced, the infants can experience a rapid catch up growth leading to excessive weight gain. Behavioral symptoms observed in children born prematurely include increased rate of hyperactivity, difficulties in concentration, and below-grade-level performance at school [16].

Premature birth affects all tissues and organs of the body, including the facial structure and both primary and permanent dentitions. Direct local trauma from endotracheal intubation may cause notching/grooves on the maxillary alveolar ridge and palatal asymmetry. This may result in an altered palatal morphology in the short term but there is insufficient evidence for any long term effects [17]. Delayed eruption and developmental defects of both the primary and permanent dentitions have also been reported. Several studies have shown that prematurity or LBW can cause both qualitative (opacities and discoloration) and quantitative (reduced thickness and hypoplasia) defects in teeth [18–20]. The extent of the defects relate to the timing of and interference with tooth development. Maternal under nutrition during pregnancy, deficiency of minerals, or medical intervention in the neonatal period may be associated with the presence of enamel defects [16]. Evidence is insufficient to establish a relationship between caries development and low birthweight [21].

Infection, pain, and sensitivity of teeth affected by caries may further diminish oral nutrient intake. A tendency to snack frequently, be faddy eaters, and have high levels of dental decay and erosion was observed in children born SGA (with no obvious comorbidities) [20]. Parents of these SGA children misinterpreted dietary advice during infancy and believed that frequent high calorie feedings would encourage catch up growth. Prolonged use of bottle feeding was common (>18 months) and frequent ingestion of high calorie foods continued even when catch up growth had been achieved. Parents admitted that oral health practices were given a low priority. The feeding practices established in infancy influenced subsequent food choices and feeding patterns. Treatment of the decayed teeth, eliminating night-time bottle feeding, and reducing the frequency of snacking, combined with improved tooth cleaning, helped establish a healthy dentition for these children.

Oromotor Dysfunction

Effective functioning of the masticatory system is a determinant for the correct growth and development of its structures. Any alteration to this balance such as a large tongue, mouth breathing, craniofacial dysmorphology, or missing or abnormal teeth may result in ineffective or uncoordinated

swallowing, and chewing [22, 23]. Macroglossia occurs commonly in Trisomy 21 but also occurs in Beckwith–Wiedeman syndrome, and the mucopolysaccaridosis. Maintenance of an oral seal requires coordination of the musculature of the tongue and lips. Oro-facial regulation therapy can be very successful in improving oromotor function in children with drooling or large tongues. In some circumstances, surgery can also be used to assist with feeding and associated problems.

Children with neurodevelopmental disorders can have challenging feeding problems due to oromotor dysfunction. These children with special health care needs will require nutritional support, which may include prolonged or frequent feeding or special diets. Premature infants often have difficulty in coordinating sucking, swallowing, and breathing. These difficulties may continue into childhood if there is interference with the development of oral skills and will influence oral intake, growth, and nutrition [22]. Professional intervention is required to maximize the potential for normal swallowing and adequate nutrient intake.

Dental Eruption

The appearance of teeth is an important developmental time for the infant and parent. Interference with breastfeeding due to erupted teeth is sometimes reported, usually where infants have natal/neonatal teeth. These teeth may physically damage the undersurface of the tongue (Riga–Fede disease) or irritate the nipple during breastfeeding. These teeth are not extra teeth and should only be extracted when excessively mobile. Natal and neonatal teeth may also indicate the presence of other anomalies and are associated with syndromes such as Hallermann-Streiff or Ellis van Creveld.

A range of systemic effects have been attributed to teething in infants such as irritability, disturbed sleep, drooling, or loss of appetite [24]. These symptoms are usually temporary and disappear once the tooth has erupted clinically. Teething symptoms should have no long term effect on nutrition for the infant, however supportive efforts by some parents can result in unsafe feeding habits such as adding sugar to feeding bottles/pacifiers and using sweetened food to pacify the baby. These practices can be detrimental and should be discouraged as they can influence subsequent feeding patterns and taste preferences [25].

Delayed dental emergence has been reported to be affected by suboptimal growth, malnutrition, low socioeconomic status, low birthweight, prenatal diseases, and developmental disabilities. Undernourished children have significantly slower skeletal maturation rates and delayed dental eruption which complicates the interpretation of studies of caries incidence in various populations [26]. Brazilian children presenting height-for-age deficit had less pairs of emerged teeth at 6 and 12 months of age and children stunted at 6 months of age were more likely to have non-emerged first upper left and lower right permanent molars at 6 years of age [27]. In contrast, well nourished and undernourished Peruvian child populations showed no effect of nourishment on mineralization of teeth [28].

Abnormal Tooth Development

When enamel or dentin formation has been disrupted, there is a possibility that the tooth will be painful or sensitive in the oral cavity, which may affect the child's ability to eat and function normally. Destruction of the second primary molars due to enamel hypoplasia occurs frequently and the risk of caries is increased. Molar incisor hypomineralisation is a common condition affecting the permanent teeth that are mineralizing within the first year of life. The etiology is unknown but illness during infancy is implicated [29]. Chemotherapy and radiation therapy for childhood malignancies can disrupt craniofacial and tooth development, especially in children under 4 years of age and may result in failure of teeth to develop or dental defects which may impact on the child's ability to eat [30].

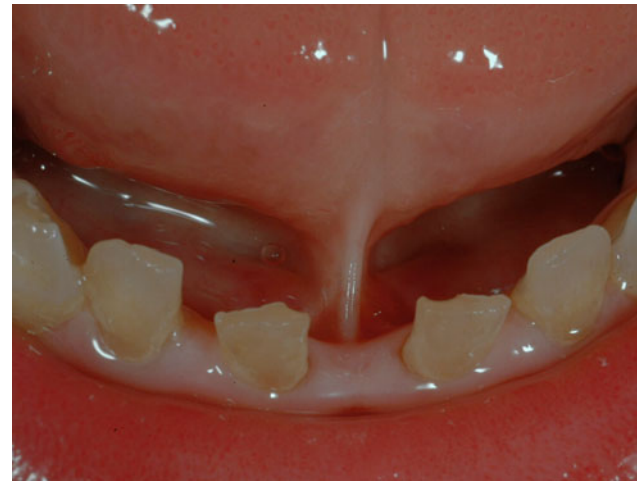

Fig. 8.2 Ankyloglossia limiting tongue movement

Absence (anodontia) or reduced number of teeth (hypodontia) can occur in syndromes or conditions, e.g. ectodermal dysplasias (Table 8.3). Most children with no other comorbidities adapt well and have no detrimental effect on their nutrition. Dental prostheses can be provided to assist in eating if necessary. Issues may arise when the absence of teeth results in prolonged infant feeding practices and failure to experiment with food of varying textures. Many children may have difficulty subsequently with food choices which may result in feeding issues in childhood. Special diets that require prolonged bottle feeding or frequent feeding can cause oral health problems in children, especially those with special health care needs.

Ankyloglossia

Successful breastfeeding may be hindered by numerous factors, and often professional assistance in infant positioning can overcome these difficulties. Ankyloglossia is a congenital anomaly diagnosed when the lingual frenum/frenulum limits mobility of the tongue (also called tongue tie, Fig. 8.2). It has been reported that infants with ankyloglossia experience difficulty with breastfeeding due to a poor latch action or problems with swallowing. This may lead to early termination of breastfeeding [31]. The medical and lactation professional community do not agree on whether ankyloglossia requires medical intervention. It is reported to occur in 1.7–5% infants and many children with ankyloglossia breastfeed without problems. No relationship was found between frenum length and breastfeeding difficulties [32] despite this, division of the fibrous attachment (frenulotomy/lingual frenectomy) is often recommended to increase mobility of the tongue [33, 34]. The NICE recommendations suggest that this procedure should be considered when problems such as nipple pain and failure to gain weight persist despite professional counseling [34, 35]. The procedure is relatively simple and usually does not require local anesthesia.

Caries and Erosion

ECC is the currently accepted term for any carious tooth in a child under 5 years of age [36] (Fig. 8.3a, b). The frequency of breast or bottle feeding may be a risk factor when combined with poor dietary habits

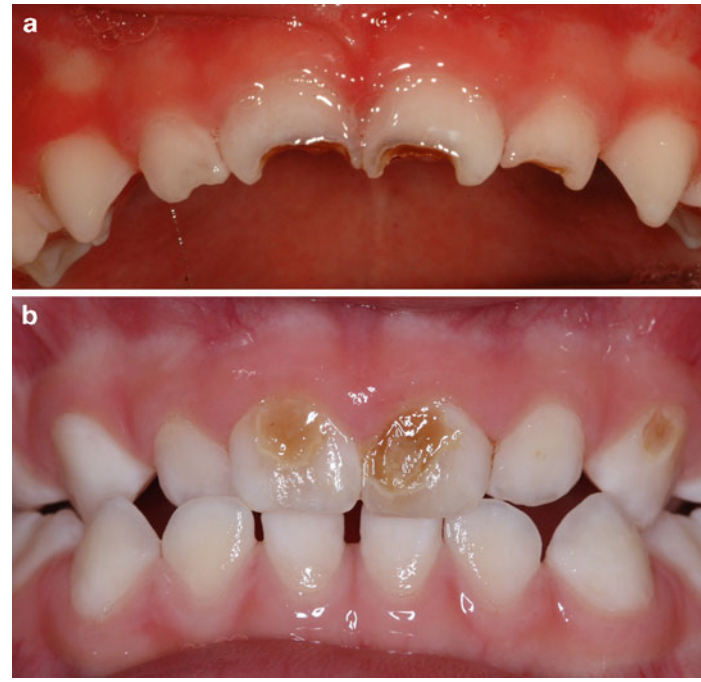

Fig. 8.3 Early childhood caries affecting the upper teeth in a distinctive pattern. (**a**) Notching of the incisal surfaces or (**b**) on the smooth surfaces at the cervical margin of the upper incisors

and inadequate tooth cleaning. Inappropriate feeding practices such as using non-milk products (juice or sweetened fluids) in feeding bottles during sleep, beyond 18 months of age and frequent snacking or 'grazing' throughout the day are commonly associated with ECC. Salivary flow is reduced during sleep so that the liquid food is not cleared effectively, allowing extended contact on the tooth surface which causes demineralization of the teeth. ECC is first recognized on the upper incisors and caries may progress rapidly on tooth surfaces not usually at risk (Fig. 8.3a, b). The lower incisors remain protected during sucking by the tongue and saliva, but will become involved if there is no intervention.

ECC is associated with prolonged on-demand feeding, especially at night, in the absence of tooth cleaning. Prolonged ad libitum breastfeeding has been implicated in ECC but recent reviews [37, 38] suggest no detrimental effects on teeth. The American Academy of Pediatric Dentistry recommends breastfeeding of infants with cessation of ad libitum breastfeeding as the first primary tooth begins to erupt and other dietary carbohydrates are introduced [39].

The introduction of solid foods usually coincides with the emergence of the first teeth. Introduction of age appropriate foods with varying consistency and texture has important implications for food preferences. Infants should be weaned from breast/bottle to cup feeding as the diet advances and this allows introduction of new foods and textures. Cow's milk (5% lactose) has been shown to be less cariogenic than either breast milk (7% lactose) or infant formulas (various concentrations of sugar) [40, 41]. Children fed for extended periods with a bottle may be less willing to accept new foods and may become faddy eaters. Parents are uneducated about the consequences of late weaning on the oral health of their children [42].

Food Exposures

Parental barriers to weaning infants from a bottle include behavioral, social, and cultural issues [42]. Limited food exposures and preferences in infancy may lead to unbalanced nutrition which may last into adolescence and adulthood. Parents influence the development of food preferences by restricting

access or pushing certain foodstuffs and tastes. Food preferences for sweet and salt with a dislike for sour taste are believed to be genetically determined. This can be modified from birth by experience, therefore parental choices play a role in the development of food aversions. A tendency to avoid novel foods often occurs in the second year of life and there is a predisposition to learn to like foods with high energy density [43].

It is known that the child assumes the eating habits of the family in the second year of life [44, 45]. Particular concern exists when the preference is for sweetened food/drink as this increases the risk for dental caries. In one study of at risk families, there was a 44% increase in caries in children with every additional soft drink consumed by the parents [4]. Parents must be supported in achieving an appropriate pattern of food intake for their child while minimizing the risk of caries.

Children with systemic illness may have an inappropriate nutrient uptake due to the underlying illness, e.g. cystic fibrosis. In addition, the illness and the medications used in management may interfere with a child's appetite. Pediatric medications may have side effects that reduce salivary flow (salivary gland hypofunction) which will increase retention of foodstuffs in the oral cavity. Importantly, many medications are sweetened with sucrose and are produced in viscous liquid form. This has given rise to the widespread belief that childhood medication is a direct cause of caries. The sucrose content of medications may increase the risk of caries only if the medication is allowed prolonged contact with the teeth. Medical practitioners should always request sugar free formulations when available and instruct parents to increase oral hygiene measures following ingestion of oral medication. Rinsing the oral cavity after ingestion of medication will remove it from the oral surfaces and lubricate oral mucosa if salivary flow is affected. Parents and caregivers of chronically ill children often use sweetened foods as rewards/bribes. Use of food in this manner should be discouraged in all health care settings. All of these factors increase the risk of caries in a child with long term illness or condition.

Effective tooth cleaning is an essential adjunct to dietary support to reduce risk of decay. Many parents believe that children as young as 3 years of age can clean their teeth effectively and often are not supervised in this essential task [20].

Pain, infection, and discomfort due to established caries may interfere with adequate food intake. It has been shown that dental caries negatively affects body weight and growth in preschool children and weight gain occurs once the disease has been treated [46, 47]. The establishment of a dental home by 1 year of age is also encouraged where the infant is comprehensively evaluated by a dentist and an individualized preventive treatment plan is delivered to the primary care giver and support offered to minimize any possible damage to oral health [48]. Caries is a disease that is readily preventable or manageable through early and regular oral health care and adoption of a health-promoting diet. Where caries risk is increased, for whatever reason, intervention and support by a dentist will minimize this risk. Evidence supports the use of topical fluoride and application of sealants to prevent disease.

Erosion is tooth surface loss that is not bacterially mediated. The loss of tooth structure results from an acidic intraoral environment from either external or internal source. An increased consumption in quantity and frequency of juices and carbonated drinks is commonly associated with erosion in children. This may have implications for the nutrition of the child as these beverages are replacing milk and water in the diet of children and may indicate a need for dietary intervention. Gastric-esophageal reflux disease (GERD) can also allow an acidic environment in the oral cavity which also complicate achieving a balanced nutrition intake.

Conclusions

Efficient functioning of the mouth, lips, and tongue facilitate oral intake for nourishment. A wide range of disabilities in children can interfere with nutrition, both as a manifestation of the disability or as a result of its management. Even when craniofacial development is normal, feeding difficulties can arise in the neonatal period due to biological, developmental, or behavioral issues. A complex

Table 8.4 Recommendations for all healthcare personnel involved in infant care

Support exclusive breastfeeding for at least 6 months
Stop ad libitum feeding once teeth erupt
Never put child to sleep with bottle
Wash teeth after night feeds
Introduce a cup before 1 year
Never use food as a reward
Offer variety of foods and textures
Limit snacking
Advise that adult needs to brush teeth up to 6 years of age
See a dentist for individualized plan (Dental home)

neurophysiological coordination of breathing, sucking, and swallowing is required for efficient oral food ingestion. Children with developmental disabilities such as autism, cerebral palsy, and other neuropathies often have difficulties around food and require specific interventions to maintain adequate nutrition. Anatomical abnormalities of the craniofacial complex may arise from genetic or environmental effects in utero or be acquired postnatally. Some of these can be corrected surgically, facilitating normal oral function. Many systemic diseases have oral and nutritional implications. The underlying disease may require specific nutritional intervention such as special diets (cystic fibrosis and inborn errors of metabolism). Other conditions necessitate frequent intakes of energy-dense supplements. Childhood illnesses can interfere with oral and tooth development.

Unfortunately, oral health is often overlooked in the medical management of chronically ill children and children with special needs and the most common oral diseases are preventable. Medical practitioners should be able to examine and recognize dental decay and erosion in infants. A brief intraoral examination to observe the oral soft tissues and the teeth may identify some issues. Recommendations should support the parent to maintain good oral health and referral to a dentist is advised for an individual prevention and treatment plan (Table 8.4). Early intervention is important to impart information on the consequences of poor feeding behaviors on the child's general and oral health. A pediatric dentist is an essential member of the medical team and can provide additional support to medical practitioners and parents from birth through adolescence.

References

1. Gahagan S. Failure to thrive: a consequence of undernutrition. Pediatr Rev. Jan 2006;27(1):e1–11.
2. U.S. Department of Health Human Services. Oral health in America: A report of the surgeon general. http://www.nidcr.nih.gov/DataStatistics/SurgeonGeneral/sgr/home.htm. Accessed Oct 2012 Rockville, MD: Department of Health and Human Services, National Institutes of Health, National Institute of Dental and Craniofacial Research; 2000.
3. Caufield PW, Griffen AL. Dental caries. An infectious and transmissible disease. Pediatr Clin North Am. 2000;47(5):1001–19.
4. Southward LH, Robertson A, Wells-Parker E, et al. Oral health status of Mississippi Delta 3- to 5-year-olds in child care: an exploratory study of dental health status and risk factors for dental disease and treatment needs. J Public Health Dent. Spring 2006;66(2):131–7.
5. Nanci A. Embryology of the head, face, and oral cavity Ten Cate's Oral Histology: development, structure and function. 7th ed. St Louis, MO: Mosby Elsevier; 2008. p. 32–56.
6. Lunt RC, Law DB. A review of the chronology of calcification of deciduous teeth. J Am Dent Assoc. Sep 1974;89(3):599–606.
7. Marks Jr SC, Gorski JP, Wise GE. The mechanisms and mediators of tooth eruption–models for developmental biologists. Int J Dev Biol. Feb 1995;39(1):223–30.

8. Slavkin H. Intrinsic molecular determinants of tooth development from specification to root formation:A review. In: Davidivitch Z, editor. The biological mechanisms of tooth eruption, resorption and replacement by implants. Boston, MA: Harvard Society for the Advancement of Orthodontics; 1994. p. 263–72.
9. Calzolari E, Pierini A, Astolfi G, Bianchi F, Neville AJ, Rivieri F. Associated anomalies in multi-malformed infants with cleft lip and palate: An epidemiologic study of nearly 6 million births in 23 EUROCAT registries. Am J Med Genet A. 2007;143(6):528–37.
10. Krapels IP, Vermeij-Keers C, Muller M, de Klein A, Steegers-Theunissen RP. Nutrition and genes in the development of orofacial clefting. Nutr Rev. Jun 2006;64(6):280–8.
11. Bessell A, Hooper L, Shaw WC, Reilly S, Reid J, Glenny AM. Feeding interventions for growth and development in infants with cleft lip, cleft palate or cleft lip and palate. Cochrane Database Syst Rev. 2011;(2):CD003315.
12. Ciminello FS, Morin RJ, Nguyen TJ, Wolfe SA. Cleft lip and palate: review. Compr Ther. Spring 2009;35(1):37–43.
13. Riley EP, Infante MA, Warren KR. Fetal alcohol spectrum disorders: an overview. Neuropsychol Rev. Jun 2011;21(2):73–80.
14. Astley SJ, Clarren SK. Measuring the facial phenotype of individuals with prenatal alcohol exposure: correlations with brain dysfunction. Alcohol Alcohol. 2001;36(2):147–59.
15. Mattson SN, Crocker N, Nguyen TT. Fetal alcohol spectrum disorders: neuropsychological and behavioral features. Neuropsychol Rev. Jun 2011;21(2):81–101.
16. O'Connell S, O'Connell A, O'Mullane E, Hoey H. Medical, nutritional, and dental considerations in children with low birth weight. Pediatr Dent. 2009;31(7):504–12.
17. Paulsson L, Bondemark L, Soderfeldt B. A systematic review of the consequences of premature birth on palatal morphology, dental occlusion, tooth-crown dimensions, and tooth maturity and eruption. Angle Orthod. Apr 2004;74(2):269–79.
18. Aine L, Backstrom MC, Maki R, et al. Enamel defects in primary and permanent teeth of children born prematurely. J Oral Pathol Med. Sep 2000;29(8):403–9.
19. Lai PY, Seow WK, Tudehope DI, Rogers Y. Enamel hypoplasia and dental caries in very-low birthweight children: a case-controlled, longitudinal study. Pediatr Dent. 1997;19(1):42–9.
20. O'Connell AC, O'Connell SM, O'Mullane E, Hoey HM. Oral health of children born small for gestational age. Ir Med J. Oct 2010;103(9):275–8.
21. Burt BA, Pai S. Does low birthweight increase the risk of caries? A systematic review. J Dent Educ. Oct 2001;65(10):1024–7.
22. Delaney AL, Arvedson JC. Development of swallowing and feeding: prenatal through first year of life. Dev Disabil Res Rev. 2008;14(2):105–17.
23. Sonnesen L, Bakke M, Solow B. Bite force in pre-orthodontic children with unilateral crossbite. Eur J Orthod. Dec 2001;23(6):741–9.
24. Macknin ML, Piedmonte M, Jacobs J, Skibinski C. Symptoms associated with infant teething: a prospective study. Pediatrics. Apr 2000;105(4 Pt 1):747–52.
25. Ismail AI. The role of early dietary habits in dental caries development. Spec Care Dentist. 1998;18(1):40–5.
26. Flores-Mir C, Mauricio FR, Orellana MF, Major PW. Association between growth stunting with dental development and skeletal maturation stage. Angle Orthod. Nov 2005;75(6):935–40.
27. Bastos JL, Peres MA, Peres KG, Barros AJ. Infant growth, development and tooth emergence patterns: A longitudinal study from birth to 6 years of age. Arch Oral Biol. Jun 2007;52(6):598–606.
28. Cameriere R, Flores-Mir C, Mauricio F, Ferrante L. Effects of nutrition on timing of mineralization in teeth in a Peruvian sample by the Cameriere and Demirjian methods. Ann Hum Biol. 2007;34(5):547–56.
29. Alaluusua S. Aetiology of Molar-Incisor Hypomineralisation: A systematic review. Eur Arch Paediatr Dent. Apr 2010;11(2):53–8.
30. Meck MM, Leary M, Sills RH. Late effects in survivors of childhood cancer. Pediatr Rev. Jul 2006;27(7):257–62. quiz 263.
31. Messner AH, Lalakea ML, Aby J, Macmahon J, Bair E. Ankyloglossia: incidence and associated feeding difficulties. Arch Otolaryngol Head Neck Surg. Jan 2000;126(1):36–9.
32. Hogan M, Westcott C, Griffiths M. Randomized, controlled trial of division of tongue-tie in infants with feeding problems. J Paediatr Child Health. 2005;41(5–6):246–50.
33. Geddes DT, Langton DB, Gollow I, Jacobs LA, Hartmann PE, Simmer K. Frenulotomy for breastfeeding infants with ankyloglossia: effect on milk removal and sucking mechanism as imaged by ultrasound. Pediatrics. Jul 2008;122(1):e188–194.
34. Division of ankyloglossia (tongue-tie) for breastfeeding. NICE. http://www.nice.org.uk/IPG149 NICE. Accessed 7 September 2011.
35. Srinivasan A, Dobrich C, Mitnick H, Feldman P. Ankyloglossia in breastfeeding infants: the effect of frenotomy on maternal nipple pain and latch. Breastfeed Med. Winter 2006;1(4):216–24.
36. Ismail AI. Prevention of early childhood caries. Community Dent Oral Epidemiol. 1998;26(1 Suppl):49–61.

37. Valaitis R, Hesch R, Passarelli C, Sheehan D, Sinton J. A systematic review of the relationship between breastfeeding and early childhood caries. Can J Public Health. 2000;91(6):411–7.
38. Ribeiro NM, Ribeiro MA. Breastfeeding and early childhood caries: a myth that survives. J Pediatr (Rio J). 2009;85(5):464–5. author reply 465–466.
39. American Academy of Pediatric Dentistry. Policy on dietary recommendations for infants, children, and adolescents. AAPD Reference manual. Ped Dent. 2011;33(6):53–4.
40. Bowen WH, Lawrence RA. Comparison of the cariogenicity of cola, honey, cow milk, human milk, and sucrose. Pediatrics. Oct 2005;116(4):921–6.
41. Bowen WH, Pearson SK, Rosalen PL, Miguel JC, Shih AY. Assessing the cariogenic potential of some infant formulas, milk and sugar solutions. J Am Dent Assoc. Jul 1997;128(7):865–71.
42. Frazier JP, Countie D, Elerian L. Parental barriers to weaning infants from the bottle. Arch Pediatr Adolesc Med. Sep 1998;152(9):889–92.
43. Benton D. Role of parents in the determination of the food preferences of children and the development of obesity. Int J Obes Relat Metab Disord. Jul 2004;28(7):858–69.
44. Fox MK, Pac S, Devaney B, Jankowski L. Feeding infants and toddlers study: What foods are infants and toddlers eating? J Am Diet Assoc. Jan 2004;104(1 Suppl 1):s22–30.
45. Siega-Riz AM, Deming DM, Reidy KC, Fox MK, Condon E, Briefel RR. Food consumption patterns of infants and toddlers: where are we now? J Am Diet Assoc. Dec 2010;110(12 Suppl):S38–51.
46. Sheiham A. Dental caries affects body weight, growth and quality of life in pre-school children. Br Dent J. 2006;201(10):625–6.
47. Acs G, Shulman R, Ng MW, Chussid S. The effect of dental rehabilitation on the body weight of children with early childhood caries. Pediatr Dent. 1999;21(2):109–13.
48. American Academy of Pediatric Dentistry. Policy on the Dental Home AAPD Reference Manual. Ped Dent. 2011;33(6):24–5.

Chapter 9
Role of Gangliosides in Neurological Development and the Influence of Dietary Sources

R. Mendez-Otero, P.M. Pimentel-Coelho, S. Ukraintsev, and P. McJarrow

Key Points

- Gangliosides are a complex family of sialic-acid-containing glycosphingolipids.
- Gangliosides are components of all vertebrate cells, with the highest concentrations being found in neural tissue.
- Gangliosides have essential roles in neurological, especially brain, development and function.
- Disorders of ganglioside synthesis and ganglioside breakdown have significant impacts on neurological function in humans.
- Foods of animal origin contain gangliosides, and human milk is an important ganglioside source for the growing child.
- Food gangliosides can affect the concentration of gangliosides in the blood.
- Gangliosides can cross the placental barrier, affecting ganglioside levels in the brain.
- Evidence (in vitro, animal and human) suggests that exogenous gangliosides (isolated or in food) can impact neurological development and function in children.

Keywords Gangliosides • Neurological development • Children • Dietary

Introduction

After over a century of investigation, gangliosides are still a group of biologically active molecules that deserve further study. That study could be from a number of perspectives, including efficacy, analysis, membrane fluidity, cell maturation, receptor interactions, cell signalling, microbial interactions, genetic disorders, nerve signalling, the immune system, structure-function interactions, commercial production and food or medicinal applications. This chapter is focused on the role that

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gangliosides have on neurological development and on the evidence available that exogenous or supplementary sources of gangliosides, such as food, can have an effect.

Background to Gangliosides

Gangliosides are a wide family of glycosphingolipids that contain one or more sialic-acid residues. They were first extracted from brain "Ganglionzellen" (ganglions or neurons), hence the name, but occur in most animal tissues and fluids including blood, amniotic fluid and milk [1–3]. The profile and the concentration of gangliosides depend on the organ, sub-region of the organ, tissue or fluid as well as on the stage of cellular development and the age of the organism. Although gangliosides are present in all vertebrate cells, they are in unusually high concentration in the cells of the nervous system which, along with their spatial and temporal patterns of distribution, has led to the suggestion that they have a special role during neurological development.

The word ganglioside hides a complex mix of molecular structures. Greater than 20 sialic-acid-containing glycan structures, or moieties, are joined to a sphingosine, which can have various carbon chain lengths and different levels of saturation. The complexity is increased further by the range of fatty acids that join the other components. In fact, gangliosides are considered to be one of the most diverse groups of lipids. Given this variety of structures, considerable consideration must be exercised when studies associated with gangliosides are compared, because different gangliosides may have different biological functions in the different tissues of the body.

Given the complexity, it is not surprising that several naming systems exist for the gangliosides. The most exact system is that of IUPAC [4], which takes into consideration glycan, sphingosine and fatty acid components. A simpler, shorter, naming system that is based exclusively on the glycan is used more extensively and was developed from the thin layer chromatography of human brain gangliosides [5]. This chapter uses this later, simpler, nomenclature because it will be more familiar to readers. Under this naming system, all ganglioside names begin with "G" and the rest of the name is based on the glycan component of the ganglioside. M, D, T and Q refer to mono-, di-, tri- and tetrasialogangliosides respectively and the numbers 1, 2, 3, etc. refer to the order of migration of the ganglioside on thin layer chromatography. For example, the order of migration of monosialogangliosides is GM3>GM2>GM1. As well, to indicate further variations in the basic structure, suffixes, such as a, b etc., are added, i.e. GM1a, GM1b, etc.

Based on their oligosaccharide structures, gangliosides can be categorized into five major families: gala, hemato, ganglio, lacto and globo series. The gala series is derived from galactosylceramide and there is only one ganglioside (GM4) in this family. All other gangliosides originate from lactosylceramide and are divided into four families according to the types of sugar linked to the galactose moiety of lactosylceramide.

Variations in sialic-acid residues also contribute to the diversity in ganglioside structures. The sialic-acid residues are present either as *N*-acetylneuraminic acid or *N*-glycolylneuraminic acid (NeuGc). NeuGc is not synthesized in humans but can be ingested in the human diet and, although the majority is excreted, a small proportion can be incorporated into glycan structures in small amounts [6].

Additional variations include *O*-acetylation of the sialic-acid residue, which can occur at the 4- or 9-hydroxyl group, and lactonization. These modifications result in a dramatic change in the function of the ganglioside. For example, the ganglioside GD3 is expressed uniformly in several regions of the developing brain. *O*-acetylation in position 9 of the sialic acid generates the ganglioside 9-*O*-acetyl GD3 (9-*O*-Ac GD3), which has a very specific temporal and spatial distribution in the developing brain. Furthermore, 9-*O*-Ac GD3 is found in melanoma cells; however, it is not found in melanocytes, which in turn express GD3.

It is possible that the 9-*O*-acetyl group is more abundant than that has been described to date but is probably missed because it is very sensitive to alkali treatments, which are a common analytical practice for isolating sphingolipids. Gangliosides with sulphate groups or that are methylated at the 8-hydroxyl group of the sialic acid have also been described and isolated from human kidney cells.

The ceramide structure is very simple and sphingosine is usually the main sphingoid base.

Ganglioside Synthesis

The de novo biosynthesis of glycosphingolipids begins in the inner leaflet of membranes in the endoplasmic reticulum–Golgi secretory pathway. The minimal motif that defines a glycosphingolipid is a monosaccharide (glucose or galactose) that is attached directly to a ceramide unit. Each of these basic units (glucosylceramide or galactosylceramide) can be further extended by the stepwise addition of further monosaccharides.

The pathways for biosynthesis of the common series of gangliosides, e.g. of the ganglio series, involve sequential activities of sialyltransferases and glycosyltransferases. It has been suggested, but not yet proven, that these enzymes are bound to the membranes of the Golgi apparatus in a sequence that corresponds to the order of addition of the various carbohydrate components.

After the Golgi apparatus, the gangliosides are transferred primarily to the external leaflet of the plasma membrane by a transport system involving vesicle formation. In the membrane, they tend to develop into specialized microdomains.

In cell types with a high concentration of gangliosides, these molecules are known to be shed from the surface and can be found in the body fluid and, in some cases, it has been shown that shed gangliosides can be taken up by other cells and incorporated into their membranes. It is not known whether such transfer can also occur in vivo.

The majority of brain gangliosides belong to the ganglio series and most adult mammalian brains contain at least four major gangliosides, i.e. GM1, GD1a, GD1b and GT1b, which account for 80–90% of the total gangliosides in the brain.

Gangliosides of the hemato series, such as GM3 and GD3, are minor components of the adult brain but are very abundant during development, as described below. GM4, the only ganglioside in the gala series, is the third most abundant ganglioside in human white matter.

Changes in Individual Gangliosides During the Stages of Neurological Development

The concentrations and distributions of brain gangliosides change dramatically during development [7]. Two well-described features during development are the general increase in total ganglioside concentration and the predominance of GM3 and GD3 during early embryonic ages. At later ages, the gangliosides of the ganglio series increase in concentration. These changes are apparently caused by a shift during development from the synthesis of simple gangliosides of the hemato series to the synthesis of more complex gangliosides.

In the human brain, it has been observed that the amount of gangliosides increases two- to threefold from the tenth gestational week to the age of 5 years. GD1a and GM1 are the gangliosides that increase more intensely and faster, specifically around term. Conversely, GT1b is the major ganglioside until the fifth gestational month, but its expression decreases rapidly to term, slowly increasing after birth and throughout life. GD3 is highly expressed in the first trimester and decreases until the end of the second trimester. GD2 decreases after the second trimester and GM2 decreases after term [8, 9].

With the development of monoclonal antibodies that react with specific gangliosides, it has been possible to describe a very interesting correlation between ganglioside expression and developmental events. For example, the expression of the ganglioside GQ1c is developmentally regulated in neuronal and glial precursor cells. Furthermore, GM2 is highly expressed in pyramidal neurons when dendritogenesis is occurring, decreasing after dendritic arbour maturation, and its accumulation in GM2 gangliosidosis is associated with ectopic dendritogenesis, as is discussed later [10]. Similar observations have also been made for GD3 and 9-*O*-Ac GD3.

In the developing brain, the ganglioside 9-*O*-Ac GD3 is expressed in a pattern that correlates with periods of cell migration in the retina, superior colliculus, cerebellum and telencephalon. In the embryonic telencephalon, it is expressed around the ventricles and in radially oriented processes [11, 12], decreasing during the first postnatal weeks. In the adult, ganglioside 9-*O*-Ac GD3 is restricted to the rostral subventricular zone (SVZ) [13, 14]. Therefore, 9-*O*-Ac GD3 can be observed in neurogenic regions of the brain throughout life.

In the same way, GD3 and GM3 are expressed around the ventricles, in radial glia cells (RGC) [15, 16]; these cells are the main neural progenitors during embryonic life. Ganglioside GD3 is also expressed in neural stem/progenitor cells (NSPC) in vitro [17].

The ganglioside composition of myelin has been studied and it has been shown that myelin from the mature brain contains a high concentration of GM1 in addition to GM4, which has been considered to be a marker for the presence of myelin in primates. Indeed, GM4 appears first in the human brain after the beginning of myelination [8].

In Vitro Evidence of Gangliosides Affecting Neural Development

Since the first observations that the addition of bovine-brain gangliosides to culture media had a potent effect in neuroblastoma cells, enhancing axonal elongation and increasing the number and the length of cell processes [18], the role of gangliosides in neuritogenesis and dendritogenesis has been further supported by several in vitro studies. For instance, GM1 induces neurite outgrowth in neuroblastoma cells [19] and immunoblockage of 9-*O*-Ac GD3 reduces neurite extension in embryonic dorsal root ganglia explants [13, 14]. In contrast, the gangliosides GD1a and GT1b bind to myelin-associated glycoprotein, presenting a role in myelin stabilization and supporting neurite outgrowth inhibition in the adult brain [20].

The biological function of gangliosides in neural development has also been demonstrated by several studies showing that the ganglioside 9-*O*-Ac GD3 is important for glial-guided neuronal migration of cerebellar granule neurons both in vitro [21, 22] and in vivo [23] and that 9-*O*-Ac GD3 immunoblockage arrests neuronal migration in embryonal carcinoma stem cell aggregates [24].

Furthermore, gangliosides might regulate synaptic transmission in the nervous system. Depletion of glycosphingolipids with the glucosylceramide synthase inhibitor D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol decreased synapse formation in cultured rat cerebral cortical neurons, as indicated by a suppression of spontaneous synchronized oscillatory activity of intracellular Ca^{2+}. This effect was reversed by supplementation of the culture medium with GQ1b, but not by supplementation with GM1, GD1b or GD3 [25]. Accordingly, GQ1b enhanced ATP-induced long term potentiation (LTP) in CA1 neurons of guinea pig hippocampal slices, in part through a modulation of NMDA receptors/Ca^{2+} channels [26]. These observations were recently confirmed using (beta) β1,4-*N*-acetylgalactosaminyltransferase ((beta) β1,4 GalNAc-T) transgenic mice, which have decreased levels of b-pathway gangliosides, including GQ1b, in the hippocampus. These mice exhibited learning deficits and an altered synaptic plasticity, as evidenced by an attenuation of the induction of LTP [27].

Recently, an increasing number of studies have examined how gangliosides exert their actions in the nervous system. Glycosphingolipids, gangliosides in particular, are important components of lipid rafts, i.e. special membrane regions in which lipids, signalling proteins and cell-adhesion molecules

are clustered. Gangliosides can interact with these proteins in lipid rafts, modulating their action in a specific manner. For instance, they can modulate the effects of growth factors, affecting the binding of these molecules with their receptors. It has been shown that the interaction of GM3 with the extracellular domain of epidermal growth factor receptor (EGFR) inhibits the autophosphorylation of EGFR [28], and that the association of GM1 with tyrosine kinase receptors potentiates the effects of nerve growth factor (NGF) on neurite outgrowth [29]. In addition, GT1b and GM1 promote the release of brain-derived neurotrophic factor in human neuroblastoma cells [30], suggesting that gangliosides can modulate the effects of neurotrophins by multiple mechanisms. Therefore, it is not surprising that gangliosides are implicated in the regulation of cell survival. For example, it has been demonstrated that GM1 promotes neuronal survival, potentiating the effects of NGF [31], and that deacetylation of endogenous 9-*O*-Ac GD3 induces apoptosis in a human glioblastoma cell line that expresses high levels of this ganglioside [32].

Roles of Various Gangliosides During the Stages of Neurological Development

Gangliosides control many steps in the development of the central nervous system (CNS), regulating processes such as apoptosis, proliferation, migration, neuritogenesis, axonogenesis, dendritogenesis and synaptic transmission.

Mice lacking the enzyme UDP-glucose:ceramide glucosyltransferase in neural cells, which is responsible for the initial step of glycosphingolipid biosynthesis, developed severe ataxia and motor impairments in the first postnatal week and died within 24 days. These mice had abnormally large peripheral nerve axons and myelin sheaths. Moreover, primary neuronal cultures from their embryonic hippocampus revealed reduced neurite outgrowth [33].

The complete absence of the ganglio series of gangliosides in double-null mice carrying mutations in the enzymes GM2/GD2 synthase (encoded by the GalNAc-T gene) and GM3 synthase (encoded by the Siat9 gene) resulted in progressive neurological impairment, beginning in the second postnatal week. The animals displayed severe neurodegeneration, axonal degeneration and vacuolization in the spinal and cerebellar white matter and died within the first 2 months [34]. However, knockout mice for the gene GalNAc-T did not present gross morphological changes in the CNS [35], although they developed axonal degeneration in the optic and sciatic nerves, decreased myelination in the CNS and demyelination in the peripheral nervous system [36]. As the brains of these mice still contained the simple gangliosides GD3 and GM3, it is possible that they could compensate for the absence of the complex ganglio series of gangliosides, suggesting a possible redundant function of different gangliosides. Similarly, mice deficient in the enzyme GD3 synthase, which lack all b- and c-series gangliosides, had an apparently normal CNS morphology. They exhibited only subtle changes, such as a decreased regenerative potential after hypoglossal nerve axotomy [37] and an abnormal pain perception [38].

Several observations also suggest that gangliosides could modulate neurogenesis and gliogenesis, by controlling basic functional properties of NSPC. During brain development, the gangliosides GD3 and 9-*O*-Ac GD3 are expressed in at least two main types of NSPC: neuroepithelial progenitors, the proliferative cells that form the pseudo-stratified epithelium of the ventricular zone [39], and RGC, which appear after the onset of neurogenesis and have some astroglial characteristics [12, 15]. Although the role of 9-*O*-Ac GD3 and GD3 in NSPC remains to be elucidated, a reduction in the proliferation of NSPC was observed after GD3 synthase overexpression in NSPC in vitro [39].

In addition, gangliosides could modulate programmed cell death, an important mechanism that controls the number of neural progenitors and postmitotic neurons during brain development [40]. Accordingly, it has been shown that intracerebroventricular administration of GM3 in neonatal animals decreases proliferation and increases the number of apoptotic cells in the SVZ, an important neurogenic region that persists throughout life. GM3 also induces the apoptosis of proliferating astrocytes and of neuronal and glial precursors in vitro [41].

Disturbances of Ganglioside Metabolism and Effects on Neurological Development

The relevant biological function of gangliosides during brain development is also suggested by the presence of marked neurological dysfunction in patients with disorders of lysosomal metabolism in which specific gangliosides accumulate in the CNS because of a deficiency in their catabolism.

GM1 gangliosidosis is an autosomal recessive lysosomal storage disorder that is due to a deficiency of the lysosomal hydrolase β-galactosidase, resulting in the accumulation of GM1 and related glycoconjugates in several tissues and particularly in the CNS. Neurodegeneration and demyelination are usually observed. Disease onset can occur between birth and 6 months and rapidly progresses, with CNS degeneration and death within the first years of life, or the disease can have a slower progression, appearing between 7 months and 3 years, retarding the cognitive development of affected children. Alternatively, a late-onset form of the disease, in which there is local deposition of GM1 in the caudate nucleus, may occur, causing an extrapyramidal disorder [42]. In contrast, one study demonstrated that GM1 has an anti-apoptotic role in striatal cell lines, through activation of the prosurvival kinase Akt, and it has been suggested that reduced levels of GM1 are involved in the pathogenesis of Huntington's disease [43]. Taken together, these observations suggest that the presence of the correct amount of GM1 is necessary to prevent apoptosis in the CNS.

GM2 gangliosidoses are genetic disorders that result from a deficiency in the enzyme (beta) β-hexosaminidase, which is responsible for the degradation of GM2 gangliosides. Tay–Sachs disease is caused by a mutation in the hexosaminidase A (HEXA) gene (which encodes the (alpha) α-subunit of (beta) β-hexosaminidase), leading to a deficiency of the A isoenzyme, whereas Sandhoff disease is caused by a mutation in the HEXB gene (which encodes the (beta) β-subunit of (beta) β-hexosaminidase), leading to a deficiency of both the A and B isoenzymes. As a result, there is progressive accumulation of GM2 in the CNS and in the peripheral autonomic nervous system in both diseases, resulting in neurodegeneration. Depending on the residual activity of the enzyme, the onset of the diseases may be varied, classifying them into infantile, juvenile and adult forms. Motor impairment, seizures, weakness and blindness are some of the symptoms that can be observed during the course of both diseases [44].

One of the key findings in the brains of patients with GM2 gangliosidosis is the presence of ectopic dendritogenesis, observed for the first time in 1975 during a Golgi analysis in a cortical biopsy from a child with a progressive form of mental retardation. Meganeurites can be observed mainly in cortical pyramidal neurons, as a result of abnormal ganglioside storage in swollen compartments at the axon hillock. These meganeurites are composed of dendritic-like membranes and long dendritic spine-covered processes emanate from them. Synapses in the surfaces of the meganeurites can also be observed [10].

Furthermore, GM2 accumulation increases the proliferation of astrocytes with a disrupted HEXB gene [45, 46]. This observation suggests that the neuropathological alterations observed in GM2 gangliosidosis are not exclusive of neurons. In this regard, microglial cell function might also be affected by the abnormal accumulation of GM2 [45, 46].

Ectopic dendritic sprouting is not unique to GM2 gangliosidosis and can be found in other storage diseases. Although a disturbance of ganglioside degradation is not the primary biochemical defect in these diseases, several studies have shown that GM2 may be involved in their pathogenesis. For instance, it was demonstrated that GM2 accumulation preceded ectopic dendritic formation in alpha-mannosidosis, mainly in a subset of pyramidal neurons that developed ectopic dendrites. However, the role of ganglioside accumulation in other storage disorders is still not completely understood. Niemann–Pick disease type C (NPC) is caused by a defect in NPC1, a transmembrane protein that is involved in the intracellular transport of cholesterol to post-lysosomal destinations. When mice carrying a mutation in NPC1 were bred with mice carrying a mutation in GalNAc-T, which encodes the enzyme that synthesizes GM2 and complex gangliosides, the characteristic neuronal storage pathology

(including abnormal storage of cholesterol) was reduced in the double mutant mice. However, it was not accompanied by an improvement in the clinical phenotype and neurodegeneration was not reduced [47]. In contrast, treatment with an inhibitor of glucosylceramide synthase, a pivotal enzyme in the early pathway of glycosphingolipid synthesis, reduced ganglioside accumulation and the neuropathological changes in murine and feline animal models of NPC [48].

Whereas gangliosidoses are caused by a disruption of ganglioside catabolism, an autosomal recessive infantile-onset symptomatic epilepsy syndrome that is caused by a defect in ganglioside biosynthesis was described for the first time by Simpson et al. [49]. They reported that a loss-of-function mutation in the gene of GM3 synthase, which is a pivotal enzyme for the synthesis of a- and b-series complex gangliosides, was observed in children from two families who presented developmental stagnation, blindness and an epilepsy syndrome. Similarly, mice with a disruption of the gene for GM2/GD2 synthase (GalNAc-T) were unable to synthesize complex gangliosides and had an increased susceptibility to kainate-induced seizures and neurodegeneration in the hippocampal CA3 region, which could be reversed by administration of LIGA-20, a semi-synthetic analogue of GM1 [50]. Moreover, double knockout mice for the GD3 synthase and the GM2/GD2 synthase, which express GM3 as the major ganglioside, developed lethal seizures in response to sound stimulus [51] and reduced levels of gangliosides were observed in the cerebral fluid of patients with West syndrome, an infantile epileptic syndrome [52].

In conclusion, the expression of gangliosides needs to be highly regulated throughout life. Disturbances in the temporal and spatial expression of gangliosides may affect the normal development of the CNS, causing severe neurological symptoms.

Dietary Sources of Gangliosides

The time frame for the diet to influence neurological development and function extends from the time of conception to old age. In some ways, brain development can be termed magical because of the amount of knowledge we do not have relating to its compositional, structural and functional aspects; it just happens. Furthermore, knowledge of dietary influences can be described as extensive but by no means complete.

One issue that is often overlooked in various publications is the extraction and analytical techniques that are used in studies and how results are expressed. As described earlier, gangliosides are a complex group of molecules but the common factors are the ceramide and the presence of sialic acid. Until very recent developments in high performance liquid chromatography-mass spectrometry technologies [53, 54], the quantification of gangliosides was limited to measuring only the amount of sialic acid and that was referred to as lipid-bound (or associated) sialic acid (LBSA or LASA); thus many studies quantified sialic acid by scanning the thin layer chromatography plate stained for sialic acid and possibly report a percentage contribution of each ganglioside group to this amount. This does not actually give an amount of each ganglioside because of the different numbers of sialic-acid residues and the range of fatty acids linked to each ganglioside. Also, in many publications, it is not possible to determine whether the relative amounts of the sialic acids were taken into consideration when the percentage of each ganglioside group was expressed. The validation of extraction is not addressed sufficiently in many publications as many studies applied the same technique for different tissues or liquids (matrix) without validating the recovery of each type of ganglioside. This is an important aspect of the analysis as the polarity of GM3 is very different from that of GQ1, because of the size of the glycan group, and this can influence partitioning in many of the extraction techniques.

During the first months of life, nutrition plays a major role not only for the physical growth but also for the cognitive development of an infant. Several clinical trials have demonstrated better cognitive development of breast-fed infants than of formula-fed infants [55, 56]. In recent years, this effect has been considered to be due mainly to the presence of long chain polyunsaturated fatty acids (LCPUFAs)

Table 9.1 Ganglioside concentration of human milk, bovine milk and infant formula

Milk source	Ganglioside (μg)/mL
Human milk	10–16[a]
Bovine milk	10–14[b]
Infant formula	2.3–16[c]

[a]Nakano [63]
[b]Nakano [63], Sorenson [53] and Fong et al. [87]
[c]Sanchez-Diaz et al. [88], Sorenson [53] and Fong et al. [87]

Table 9.2 Ganglioside contents of some foods

Food	LBSA (μg)/g or mL	Reference
1% fat milk	0.5	Pham et al. [84]
Yoghurt	0.7	Pham et al. [84]
Yoghurt	5.4 (dry weight)	Moore et al. [83]
Cheddar cheese	0.7	Pham et al. [84]
Sweet buttermilk	6.6 (dry weight)	Moore et al. [83]
Cultured buttermilk	3.9 (dry weight)	Moore et al. [83]
Whole milk	0.7 (dry weight)	Moore et al. [83]
Skim milk	0.03, 0.12 (dry weight)	Moore et al. [83]
Tuna	0.8	Pham et al. [84]
Ground beef	1.6[a]	Pham et al. [84]
Egg yolk	1.7	Pham et al. [84]
Egg yolk	0.7 mg ganglioside/g	Li et al. [85]
Chicken liver	102	Shiraishi and Uda [86]

[a]Average of cooked and raw. Moore et al. [83]

in breast milk, which are absent from unsupplemented infant formulae (IFs). For more than a decade, the role of docosahexaenoic acid (DHA) has been studied in relation to an infant's cognitive development. As a result, most IFs (including formulae for healthy term infants) today are supplemented with DHA for "better cognitive and visual function development". However, the lipid composition of breast milk (as well as of an infant's brain) is far more complex, containing, apart from LCPUFAs, complex lipids, cholesterol, gangliosides, cerebrosides and others.

This leads to the question "What are the other lipids that may also have an effect on brain development?" It is well known that most of the accretion of DHA to neural tissue occurs during the last trimester of pregnancy, whereas the concentration of gangliosides in the developing human brain increases by 300% from as early as the 15th week of foetal life to the age of 6 months [57]. The hippocampus, which is responsible for memory and learning processes in the human brain, shows a 30% increase in ganglioside concentration between weeks 16 and 22 of gestation [58]. The fact that gangliosides start accumulating in the brain of a human foetus at such early developmental stages indicate that they may play important role in the complex process of the development of brain structure and function. Prenatally, the maternal diet is the source of exogenous gangliosides for the foetus.

After birth, breast milk becomes the main dietary source of gangliosides for the infant's brain. The degree of de novo synthesis has not been determined but it has been demonstrated that the concentration of gangliosides and glycoprotein sialic acid in the brains of breast-fed infants is significantly higher than that in infants fed with unsupplemented IFs [59]. As Table 9.1 shows, historical analyses of bovine milk and human milk indicate similar concentrations. The actual figures must be considered in the light of the analytical techniques but, when compared using similar techniques, human milk contains a higher concentration of gangliosides than the majority, if not all, of the IFs on the market today. Within IFs, there is a major variation in the concentration of gangliosides, ranging from zero in soy-based IFs to the greatest concentration in high quality whey-dominated IFs with ganglioside supplementation. Until recently, very few data on the ganglioside content of a range of foods have been available and even now the data are limited (Table 9.2). Milk and milk products (Tables 9.1 and

9.2) have been best characterized but further work is still required to obtain a more definitive position for these products. As Table 9.2 shows, the range of foods for which data are available is small. As plants do not synthesize sialic acid, no gangliosides are found in plant foods.

In Vivo Evidence of Exogenous Ganglioside Sources Influencing Neurological Development

Rahman [60] provides a convincing argument for the role of gangliosides in facilitating memory formation. However, for dietary gangliosides to be able to have any effect on neurological development, there are three major prerequisites.

1. They must have the ability to survive in the gastrointestinal tract.
2. They must be able to be absorbed from the gastrointestinal tract.
3. They must reach the brain by crossing the blood–brain barrier.

In addition to these prerequisites, gangliosides must be able to cross the placenta in order to support the brain development of the foetus in utero. All these prerequisites have been addressed in the scientific literature either by using animal models or by performing human trials.

That diet can influence cognition was demonstrated in a recent study by Crichton et al. [61], which showed that frequent dairy food intake is associated with better cognitive performance, even though the underlying mechanisms or ingredients that were responsible for this effect were not determined. With respect to gangliosides from dairy foods surviving the gastrointestinal tract, Idota and Kawakami [62] showed that at least 80% of GD3 and GM3 from human milk remained intact after passing through the acidic conditions in the infant's stomach and subsequently reached lower parts of the gastrointestinal tract. This survivability was confirmed by measuring the concentration of glycolipids in the faeces of breast-fed infants; it was shown that the ganglioside content of the faeces reflected the ganglioside content in the breast milk [63]. Nevertheless, some losses in gangliosides and sialic acid occur during the gastric and intestinal phases of digestion [64], which needs to be considered when supplementing paediatric or other formulations with gangliosides.

The further fate of dietary gangliosides is more complex. They can be absorbed in the small intestine [65] and be either incorporated into enterocytes or transported to different tissues in the body.

Once gangliosides reach the targeted tissue, their structure will be remodelled according to the specific ganglioside needs in the particular tissue at the particular age of the individual. In the intestine, differences in ganglioside composition and concentration may have an influence on gut development and protection; for example, dietary gangliosides have the ability to support gut integrity by inhibiting the degradation of tight junction proteins during acute inflammation [66] or infection.

Either intact or remodelled gangliosides do reach the blood; the total ganglioside level in rat plasma increased after dietary ganglioside supplementation [65]. It was unclear whether this increase in blood gangliosides was a result of the same gangliosides being absorbed from the gut and transported to the blood intact or was largely a result of their remodelling in the enterocytes. The results for infants who were fed conventional IF, IF supplemented with bovine-milk gangliosides or human milk for 24 weeks indicates that remodelling prior to transport to the bloodstream occurs. This is because the actual blood ganglioside GM3:GD3 ratio [67] did not change significantly even though the conventional IF and the supplemented IF were ganglioside GD3 dominant whereas, at this stage in lactation, human milk is becoming or is ganglioside GM3 dominant [63].

The brain contains 15 times more gangliosides than visceral organs [68], and their concentration increases rapidly at very early stages of gestation. In addition to the indirect evidence, the ability of gangliosides to cross the human placenta has been confirmed directly by using an ex vivo model of dually perfused isolated human placenta lobules. It was demonstrated that bovine-milk-derived

gangliosides GM3 and GD3 were taken up from the maternal perfusate, with a consequent increase in their concentration on the foetal side [69]. Studies in rats supported this, with injected radiolabelled GM1 leading to the radiolabel being present in a number of tissues including the maternal and foetal brains, with placental transfer being as rapid as 30 min [70]. This also shows that gangliosides do cross the blood–brain barrier.

After birth, breast milk or IF becomes the main source of nutrients for the rapidly growing infant. IFs contain significantly lower amounts of gangliosides than human milk and have great variability in their composition and concentration, and to a large extent reflect the ganglioside composition of cow's milk [71]. These differences in ganglioside concentration in human milk and IF are reflected in the ganglioside concentrations in the brains of infants. Wang et al. [59] measured ganglioside and protein-bound sialic acid in the frontal cortex of infants who had died from sudden infant death syndrome. They reported that the infants fed human milk had, on average, 32% higher brain ganglioside content ($P=0.013$). Protein-linked sialic-acid concentrations were also higher ($P=0.01$) in infants fed human milk than in infants fed IF.

Whether these differences in ganglioside concentration have any influence on brain development and performance is not entirely clear but indications are that they may. Clinical trials demonstrate better cognitive development of breast-fed infants than of formula-fed infants [55, 56], which could suggest that gangliosides may play an important role in this process; however, the same could be said for many molecules, such as sialic acid, sphingomyelin and other phospholipid species that are lower in concentration in IFs.

Several animal trials have been performed to investigate this question; although the results were as variable as the trial designs, most supported the hypothesis that dietary gangliosides can improve cognitive function in rats. Inconsistent results may have been due to variations in the composition of the gangliosides tested, their dosage and the tests used to access cognitive function. In some trials, gangliosides derived from bovine brain were used [72, 73], with mixed results being obtained. One such trial, in which either bovine-brain-derived ganglioside or placebo was injected into rats at different ages, showed that gangliosides significantly enhanced the learning ability of neonatal, adult and aged rats. Likewise, the results of memory tests showed that there was a significant difference in memory retention between ganglioside-treated rats and rats receiving placebo [74]. GM1 has been the focus of experimentation because of its possible pharmaceutical applications as a neuroprotective agent and because it has also been shown to prevent seizures and oxidative stress induced in rats by glutaric acid and pentylenetetrazole [75]. Of more interest are the animal trials in which milk-derived gangliosides were used because milk seems to be a more appropriate source of gangliosides than bovine brain for infant nutrition. Animal trials in which bovine-milk-derived gangliosides were used showed significant increases in total brain, retina and intestinal mucosa ganglioside concentrations [65, 76, 77], which confirms their ability to reach the brain from the diet regardless of whether the animal consumes or is in utero and its mother consumes. Vickers et al. [78] supplemented rats with a complex milk lipid containing gangliosides from an early age, through weaning and on to young adulthood. Although the brain ganglioside concentrations were not significantly increased, the study showed that the supplementation improved cognitive measures of novelty recognition and spatial memory.

Very few human clinical trials in this area have been performed but those available suggest that there is a basis for the hypothesis that exogenous or dietary gangliosides can influence neurological development and measures of cognition. In one large trial, Xu and Zhu [79] reported evidence of the effects of exogenous and orally administered gangliosides on the brain functions of 2,230 children suffering from cerebral palsy. They reported that the oral ganglioside treatment improved the neurological symptoms associated with cerebral palsy, in particular muscle tension, limb function, language ability and intelligence. The authors stated that treatment resulted in a faster improvement with younger children (0–3 years). In older people, a 5-year ganglioside GM1 treatment study with Parkinson sufferers found that treatment led to significantly lower motor and activities of daily living scores on the Unified Parkinson's Disease Rating Scale [80]. A small trial (42 treatment and 30 con-

trol) on low-birth-weight infants studied the effect of intravenous GM1 using the Gesell scale to assess neurobehaviour and found significant improvement in neurobehaviour at 6 and 12 months, especially with respect to gross and fine movement [81]. Another small study [82] showed that supplementing an IF with bovine-milk-derived gangliosides (mainly GD3) increased serum gangliosides over those in the unsupplemented formula to those of human-milk-fed babies and that measures of cognitive development on the Griffiths scale (hand-eye co-ordination and performance IQ) were significantly improved over those of the unsupplemented IF group and were not significantly different from those of the human-milk-fed group.

In conclusion, the experimental evidence points to dietary gangliosides being able to meet the three requirements of surviving the gastrointestinal tract, being absorbed and being transported to the brain of the consumer or, in the case of a pregnant mother, to the brain of the foetus. The evidence from animal and human studies also indicates that supplementation could have an effect on neurological development or cognitive functioning.

Clearly, more clinical trials are needed to further confirm the ability of dietary gangliosides to improve cognitive development, but the results that are already available show that this is an encouraging area for further research. Not only formula-fed infants (especially premature infants and infants suffering neurological damage at birth) but also adults and elderly people should be included in such trials. Although infancy is a critical period for the development of brain and cognitive function, adulthood and ageing are the periods in life when cognitive function starts to decline and dietary gangliosides may play an important role in supporting better cognitive performance.

References

1. Klenk E. Uber die Ganglioside, eine neue Gruppe von zukkerhaltigen Gehirnlipoiden. Z Physiol Chem. 1942;273:76–86.
2. Wiegandt H. Gangliosides. In: Wiegandt H, editor. Glycolipids. Amsterdam: Elsevier; 1985. p. 101–98.
3. Rueda R, Gil A. Role of gangliosides in infant nutrition. In: Huang YS, Sinclair AJ, editors. Lipids in Infant Nutrition. Champaign, IL: AOCS; 1998. p. 213–34.
4. IUPAC (Moss GP). Nomenclature of glycolipids (recommendations 1997). http://www.chem.qmul.ac.uk/iupac/misc/glylp.html. Accessed September 19, 2011.
5. Svennerholm L. Chromatographic separation of human brain gangliosides. J Neurochem. 1963;10:613–23.
6. Tangvoranuntakul P, Gagneux P, Diaz S, et al. Human uptake and incorporation of an immunogenic nonhuman dietary sialic acid. Proc Natl Acad Sci U S A. 2003;100:12045–50.
7. Yu RK, Macala LJ, Taki T, Weinfield HM, Yu FS. Developmental changes in ganglioside composition and synthesis in embryonic rat brain. J Neurochem. 1988;50:1825–9.
8. Svennerholm L, Boström K, Fredman P, Månsson JE, Rosengren B, Rynmark BM. Human brain gangliosides: developmental changes from early fetal stage to advanced age. Biochim Biophys Acta. 1989;1005:109–17.
9. Kracun I, Rosner H, Drnovsek V, Heffer-Lauc M, Cosović C, Lauc G. Human brain gangliosides in development, aging and disease. Int J Dev Biol. 1991;35:289–95.
10. Walkley SU. Neurobiology and cellular pathogenesis of glycolipid storage diseases. Philos Trans R Soc Lond B. 2003;358(1433):893–904.
11. Blum AS, Barnstable CJ. O-acetylation of a cell-surface carbohydrate creates discrete molecular patterns during neural development. Proc Natl Acad Sci U S A. 1987;84:8716–20.
12. Mendez-Otero R, Schlosshauer B, Barnstable CJ, Constantine-Paton M. A developmentally regulated antigen associated with neural cell and process migration. J Neurosci. 1988;8:564–79.
13. Mendez-Otero R, Friedman JE. Role of acetylated gangliosides on neurite extension. Eur J Cell Biol. 1996;71:192–8.
14. Mendez-Otero R, Cavalcante LA. Expression of 9-O-acetylated gangliosides is correlated with tangential cell migration in the rat brain. Neurosci Lett. 1996;204:97–100.
15. Cammer W, Zhang H. Ganglioside GD3 in radial glia and astrocytes in situ in brains of young and adult mice. J Neurosci Res. 1996;46:18–23.
16. Stojiljković M, Blagojević T, Vukosavić S, et al. Ganglioside GM1 and GM3 in early human brain development: an immunocytochemical study. Int J Dev Neurosci. 1996;14:35–44.

17. Nakatani Y, Yanagisawa M, Suzuki Y, Yu RK. Characterization of GD3 ganglioside as a novel biomarker of mouse neural stem cells. Glycobiology. 2010;20:78–86.
18. Roisen FJ, Bartfeld H, Nagele R, Yorke G. Ganglioside stimulation of axonal sprouting in vitro. Science. 1981;214(4520):577–8.
19. Singleton DW, Lu CL, Roisen FJ. Promotion of neurite outgrowth by protein kinase inhibitors and ganglioside GM1 in neuroblastoma cells involves MAP kinase ERK ½. Int J Dev Neurosci. 2000;18:797–805.
20. Vyas AA, Patel HV, Fromholt SE, et al. Gangliosides are functional nerve cell ligands for myelin-associated glycoprotein (MAG), an inhibitor of nerve regeneration. Proc Natl Acad Sci U S A. 2002;99:8412–7.
21. Mendez-Otero R, Constantine-Paton M. Granule cell induction of 9-O-acetyl gangliosides on cerebellar glia in microcultures. Dev Biol. 1990;138:400–9.
22. Santiago MF, Berredo-Pinho M, Costa MR, Gandra M, Cavalcante LA, Mendez-Otero R. Expression and function of ganglioside 9-O-acetyl GD3 in postmitotic granule cell development. Mol Cell Neurosci. 2001;17:488–99.
23. Santiago MF, Costa MR, Mendez-Otero R. Immunoblockage of 9-O-acetyl GD3 ganglioside arrests the in vivo migration of cerebellar granule neurons. J Neurosci. 2004;24:474–8.
24. Santiago MF, Liour SS, Mendez-Otero R, Yu RK. Glial-guided neuronal migration in P19 embryonal carcinoma stem cell aggregates. J Neurosci Res. 2005;81:9–20.
25. Mizutani A, Kuroda Y, Muramoto K, Kobayashi K, Yamagishi K, Inokuchi J. Effects of glucosylceramide synthase inhibitor and ganglioside GQ1b on synchronous oscillations of intracellular Ca2+ in cultured cortical neurons. Biochem Biophys Res Commun. 1996;222:494–8.
26. Fujii S, Igarashi K, Sasaki H, et al. Effects of the mono- and tetrasialogangliosides GM1 and GQ1b on ATP-induced long-term potentiation in hippocampal CA1 neurons. Glycobiology. 2002;12:339–44.
27. Ikarashi K, Fujiwara H, Yamazaki Y, et al. Impaired hippocampal long-term potentiation and failure of learning in {beta}1,4-N-acetylgalactosaminyltransferase gene transgenic mice. Glycobiology. 2011;21:1373–81.
28. Miljan EA, Meuillet EJ, Mania-Farnell B, et al. Interaction of the extracellular domain of the epidermal growth factor receptor with gangliosides. J Biol Chem. 2002;277:10108–13.
29. Mutoh T, Tokuda A, Miyadai T, Hamaguchi M, Fujiki N. Ganglioside GM1 binds to the Trk protein and regulates receptor function. Proc Natl Acad Sci U S A. 1995;92:5087–91.
30. Lim ST, Esfahani K, Avdoshina V, Mocchetti I. Exogenous gangliosides increase the release of brain-derived neurotrophic factor. Neuropharmacology. 2011;60:1160–7.
31. Huang F, Dong X, Zhang L, et al. The neuroprotective effects of NGF combined with GM1 on injured spinal cord neurons in vitro. Brain Res Bull. 2009;79:85–8.
32. Malisan F, Franchi L, Tomassini B, et al. Acetylation suppresses the proapoptotic activity of GD3 ganglioside. J Exp Med. 2002;196:1535–41.
33. Jennemann R, Sandhoff R, Wang S, et al. Cell-specific deletion of glucosylceramide synthase in brain leads to severe neural defects after birth. Proc Natl Acad Sci U S A. 2005;102:12459–64.
34. Yamashita T, Wu YP, Sandhoff R, et al. Interruption of ganglioside synthesis produces central nervous system degeneration and altered axon-glial interactions. Proc Natl Acad Sci U S A. 2005;102:2725–30.
35. Takamiya K, Yamamoto A, Furukawa K, et al. Mice with disrupted GM2/GD2 synthase gene lack complex gangliosides but exhibit only subtle defects in their nervous system. Proc Natl Acad Sci U S A. 1996;93:10662–7.
36. Sheikh KA, Sun J, Liu Y, et al. Mice lacking complex gangliosides develop Wallerian degeneration and myelination defects. Proc Natl Acad Sci U S A. 1999;96:7532–7.
37. Okada M, Itoh Mi M, Haraguchi M, et al. b-series Ganglioside deficiency exhibits no definite changes in the neurogenesis and the sensitivity to Fas-mediated apoptosis but impairs regeneration of the lesioned hypoglossal nerve. J Biol Chem. 2002;277:1633–6.
38. Handa Y, Ozaki N, Honda T, et al. GD3 synthase gene knockout mice exhibit thermal hyperalgesia and mechanical allodynia but decreased response to formalin-induced prolonged noxious stimulation. Pain. 2005;117:271–9.
39. Yanagisawa M, Liour SS, Yu RK. Involvement of gangliosides in proliferation of immortalized neural progenitor cells. J Neurochem. 2004;91:804–12.
40. Kuan CY, Roth KA, Flavell RA, Rakic P. Mechanisms of programmed cell death in the developing brain. Trends Neurosci. 2000;23:291–7.
41. Nakatsuji Y, Miller RH. Selective cell-cycle arrest and induction of apoptosis in proliferating neural cells by ganglioside GM3. Exp Neurol. 2001;168:290–9.
42. Brunetti-Pierri N, Scaglia F. GM1 gangliosidosis: review of clinical, molecular, and therapeutic aspects. Mol Genet Metab. 2008;94:391–6.
43. Maglione V, Marchi P, Di Pardo A, et al. Impaired ganglioside metabolism in Huntington's disease and neuroprotective role of GM1. J Neurosci. 2010;30:4072–80.
44. Jeyakumar M, Butters TD, Dwek RA, Platt FM. Glycosphingolipid lysosomal storage diseases: therapy and pathogenesis. Neuropathol Appl Neurobiol. 2002;28:343–57.
45. Kawashima N, Tsuji D, Okuda T, Itoh K, Nakayama K. Mechanism of abnormal growth in astrocytes derived from a mouse model of GM2 gangliosidosis. J Neurochem. 2009;111:1031–41.

46. Kawashita E, Tsuji D, Kawashima N, Nakayama K, Matsuno H, Itoh K. Abnormal production of macrophage inflammatory protein-1alpha by microglial cell lines derived from neonatal brains of Sandhoff disease model mice. J Neurochem. 2009;109:1215–24.
47. Liu Y, Wu YP, Wada R, et al. Alleviation of neuronal ganglioside storage does not improve the clinical course of the Niemann-Pick C disease mouse. Hum Mol Genet. 2000;9:1087–92.
48. Zervas M, Somers KL, Thrall MA, Walkley SU. Critical role for glycosphingolipids in Niemann-Pick disease type C. Curr Biol. 2001;11:1283–7.
49. Simpson MA, Cross H, Proukakis C, et al. Infantile-onset symptomatic epilepsy syndrome caused by a homozygous loss-of-function mutation of GM3 synthase. Nat Genet. 2004;36:1225–9.
50. Wu G, Lu ZH, Wang J, et al. Enhanced susceptibility to kainate-induced seizures, neuronal apoptosis, and death in mice lacking gangliotetraose gangliosides: protection with LIGA 20, a membrane-permeant analog of GM1. J Neurosci. 2005;25:11014–22.
51. Kawai H, Allende ML, Wada R, et al. Mice expressing only monosialoganglioside GM3 exhibit lethal audiogenic seizures. J Biol Chem. 2001;276:6885–8.
52. Izumi T, Ogawa T, Koizumi H, Fukuyama Y. Low levels of CSF gangliotetraose-series gangliosides in West syndrome: implication of brain maturation disturbance. Pediatr Neurol. 1993;9:293–6.
53. Sorensen LK. A liquid chromatography/tandem mass spectrometric approach for the determination of gangliosides GD3 and GM3 in bovine milk and infant formulae. Rapid Commun Mass Spectrom. 2006;20:3625–33.
54. Fong B, et al. Liquid chromatography-high-resolution mass spectrometry for quantitative analysis of gangliosides. Lipids. 2009;44(9):867–74.
55. Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. BMJ. 1998;317:1481–7.
56. Isaacs EB, Firshl BR, Quinn BT, et al. Impact of breast milk on IQ, brain size and white matter development. Pediatr Res. 2010;67:357–62.
57. Vanier MT, Holm M, Ohman R, Svennerholm L. Developmental profiles of gangliosides in human and rat brain. J Neurochem. 1971;18:581–92.
58. Kracun I, Rosner H, Drnovsek V, et al. Gangliosides in the human brain development and aging. Neurochem Int. 1992;20:421–31.
59. Wang B, McVeagh P, Petocz P, Brand-Miller J. Brain ganglioside and glycoprotein sialic acid in breastfed compared with formula-fed infants. Am J Clin Nutr. 2003;78:1024–9.
60. Rahman H. Brain gangliosides and memory formation. Behav Brain Res. 1995;66:105–16.
61. Crichton GE, Elias MF, Dore GA, Robbins MA. Relation between dairy food intake and cognitive function: the Maine-Syracuse Longitudinal Study. Int Dairy J. 2012;22:15–23. doi:10.1016/j.idairyj.2011.08.001.
62. Idota T, Kawakami H. Inhibitory effects of milk gangliosides on the adhesion of Escherichia coli to human carcinoma cells. Biosci Biotechnol Biochem. 1995;59:69–72.
63. Nakano T, Sugawara M, Kawakami H. Sialic acid in human milk: composition and functions. Acta Paediatr Taiwan. 2001;42:11–7.
64. Lacomba R, Salcedo J, Alegriá A, et al. Effect of simulated gastrointestinal digestion on sialic acid and gangliosides present in human milk and infant formulas. J Agric Food Chem. 2011;59:5755–62.
65. Park EJ, Suh M, Ramanujam K, Steiner K, Begg D, Clandinin MT. Diet-induced changes in membrane gangliosides in rat intestinal mucosa, plasma and brain. J Pediatr Gastroenterol Nutr. 2005;40:487–95.
66. Park EJ, Thomson ABR, Clandinin MT. Dietary ganglioside protects the degradation of occludin tight junction protein in acute intestinal inflammation by decreasing nitric oxide and increasing interleukin 10 production in the rat. J Pediatr Gastroenterol Nutr. 2007;44:119.
67. Gurnida D, Fong B, McJarrow P, Rowan A, Norris C. Poster presented at: World Dairy Summit. New Zealand: Auckland; 2010.
68. Wang B, Brand-Miller J. The role and potential of sialic acid in human nutrition. Eur J Clin Nutr. 2003;57:1351–69.
69. Mitchell MD, Henare K, Lowe E, Naylor M, Fong B, McJarrow P. Transfer of gangliosides across the human placenta. Early Hum Dev. 2012;33:312–6.
70. Hungund BL, Morishima HO, Gokhale VS, Cooper TB. Placental transfer of (3H)-GM1 and its distribution to maternal and fetal tissues of the rat. Life Sci. 1993;53:113–9.
71. Pan XL, Izumi T. Variation of the ganglioside compositions of human milk, cow's milk and infant formulas. Early Hum Dev. 2000;57:25–31.
72. Abraham RR, Abraham RM, Wynn V. A double blind placebo controlled trial of mixed gangliosides in diabetic peripheral and autonomic neuropathy. Adv Exp Med Biol. 1984;174:607–24.
73. Bradley WG. Double-blind controlled trial of purified brain gangliosides in amyotrophic lateral sclerosis and experience with peripheral neuropathies. Adv Exp Med Biol. 1984;174:565–73.
74. Mei ZT, Zheng J-Z. Effects of exogenous gangliosides on learning and memory in rats. Jpn J Physiol. 1993;43 suppl 1:S295–9.

75. Fighera MR, Royes LFF, Furian AF, et al. GM1 ganglioside prevents seizures, Na+, K+-ATPase activity inhibition and oxidative stress induced by glutaric acid and pentylenetetrazole. Neurobiol Dis. 2006;22:611–23.
76. Park EJ, Suh M, Clandinin MT. Dietary ganglioside and long-chain polyunsaturated fatty acids increase ganglioside GD3 content and alter the phospholipid profile in neonatal rat retina. Invest Ophthalmol Vis Sci. 2005;46:2571–5.
77. Gustavsson M, Hodgkinson SC, Fong B, et al. Maternal supplementation with a complex milk lipid mixture during pregnancy and lactation alters neonatal brain lipid composition but lacks effect on cognitive function in rats. Nutr Res. 2010;30:279–89.
78. Vickers MH, Guan J, Gustavsson M, et al. Supplementation with a mixture of complex lipids derived from milk to growing rats results in improvements in parameters related to growth and recognition. Nutr Res. 2009;29:426–35.
79. Xu X-Z, Zhu T-C. Effect of ganglioside in repairing the neurological function of children with cerebral palsy: analysis of the curative efficacy in 2230 cases. Chin J Clin Rehab. 2005;9:122–3 [in Chinese].
80. Schneider JS, Sendek S, Daskalakis C, Cambi F. GM1 ganglioside in Parkinson's disease: results of a five year open study. J Neurol Sci. 2010;292:45–51.
81. Wu C-Y, Bai L, Wang W-L, et al. Neurobehavior effect of GM-1 on LBW infants. Hei Long Jiang Med J. 2010;34:410–2.
82. Gurnida et al. Association of complex lipids containing gangliosides with cognitive development in 6-month-old infants. Early Hum Dev. 2012;88:595–601.
83. Moore HM, Ettinger AC, Yokoyama MT. Variation in ganglioside content of bovine dairy products. J Food Compost Anal. 2000;13:783–90.
84. Pham PH, Duffy LT, Dymtrash AL, Lien VW, Thomson AB, Clandinin MT. Estimate of dietary ganglioside intake in a group of healthy Edmontonians based on selected foods. J F Comp Anal. 2011;24:1032–7.
85. Li S-C, Chien J-L, Wan CC, Li Y-T. Occurence of glycosphingolipids in chicken egg yolk. Biochem J. 1978; 173:697–99.
86. Shiraishi T, Uda Y. Characterization of neutral sphingolipids and gangliosides from chicken liver. J Biochem. 1986; 100:553–61.
87. Fong B, Norris C, McJarrow P. Liquid chromatography-high-resolution electrostatic ion-trap mass spectrometry analysis of GD(3) ganglioside in dairy products. Int Dairy J. 2011;21:42–7.
88. Sanchez-Diaz A, Ruano M-J, Lorente F, Hueso P. A critical analysis of total sialic acid and sialoglycoconjugate contents of bovine milk-based infant formulas. JPGN. 1997;24:405–10.

Chapter 10
Dietary Methods to Treat Acute Gastroenteritis

Sylvia del Castillo and Kirsti Catton

Key Points

- Diarrhea, as defined by the World Health Organization (WHO), is the passage of three or more loose or watery stools per day, with chronic diarrhea defined as stool volume of more than 10 g/kg/day in infants and toddlers, or more than 200 g/day in older children for more than 14 days.
- Gastroenteritis is the single most common disorder seen in the emergency department, and the vast majority of cases are viral in origin.
- Most children who present with acute diarrhea with minimal dehydration do not require further laboratory evaluation.
- Historically, dehydration is divided into three classes depending on the percent of fluid deficit: mild (3–5%), moderate (6–9%), and severe (≥10%, with signs of shock).
- The four major recommendations in the guidelines to treat acute gastroenteritis are as follows:
- Rapid oral rehydration for 3–4 h with a hypoosmolar solution (Sodium 60 mmol/L).
- Refeeding after 4 h of rehydration with the patient's normal diet, including solids, full-strength formula or milk, with no restriction of lactose intake.
- Avoidance of unnecessary medications.
- Avoidance of microbiological investigations.
- The routine use of antimicrobial agents in the treatment of acute diarrhea may predispose the patient to antimicrobial resistance, and is not recommended.
- Probiotics have been defined as "functional food" therapy, and are thought to have an effect on the physiologic process of intestinal healing in addition to the nutritional value.

Keywords Gastroenteritis • Viral enteritis • Dehydration • Oral rehydration • Refeeding • Dietary therapy • Probiotics

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Introduction

Acute gastroenteritis is one of the most common illnesses seen in children in the USA. It is the most common infectious disease syndrome in humans rivaled only by respiratory tract infections. Five billion cases occur worldwide annually accounting for 15–30% of all deaths in developing countries [1]. Close to five million cases of gastroenteritis occur annually in the USA alone, with four million cases seen by a healthcare provider [1, 2]. Gastroenteritis (GE) is the single most common disorder seen in the emergency department (ED). It can be the result of infectious agents such as viruses, bacteria, protozoa, or parasitic infections, or as a result of other non-gastrointestinal illness Table 10.1 [2–4]. The vast majority of the cases of GE (60% of mild cases in children aged 2 months to 2 years, and 80% of moderate to severe diarrhea) are viral in origin. Proven pathogens include rotavirus (the most common), caliciviruses, astroviruses, enteric adenovirus serotypes 40 and 41 (group F), and some picornaviruses (Aichi virus). A smaller percentage of these cases are bacterial in origin such as those caused by *Escherichia coli*, *Salmonella, Shigella, Vibrio* species and *Clostridium difficile*. Recent advances in public health infrastructure have dramatically reduced the incidence of bacterial and parasitic GE in developing countries with improvements in the treatment and delivery of water [1]. Tragically, viral GE has not demonstrated the same decline.

Pathophysiology of Diarrhea

The human digestive tract is a highly efficient system designed to absorb large amounts of essential water, primarily in the small intestine. When operating under ideal conditions, the small and large intestine are capable of absorbing 99% of ingested water leaving only about 100 mL of the average intake of 8 L a day [5, 6]. This absorption is a result of three distinct mechanisms: Neutral sodium chloride absorption, electrogenic sodium absorption, and sodium co-transport [5, 6]. Because the absorptive process for water and electrolytes predominates over secretion, humans benefit from net water absorption. In the small intestine, passive transport of water occurs as a result of cation and anion exchanges (neutral sodium chloride absorption) and sodium co-transport (the coupling of absorption of water with the absorption of organic solutes such as glucose, amino acids, and peptides). In the colon, active transport is achieved through the Na/K ATPase electrochemical gradient. A disruption in the intestinal tract as a result of infectious agents or chemical agents can alter the neutral sodium chloride and electrogenic sodium absorption mechanics, although sodium co-absorption remains intact, thus the reason oral rehydration therapy works during acute diarrheal illness [5, 6].

Table 10.1 Infectious causes of acute infectious diarrhea

Viral	Bacterial	Parasitic
Rotavirus	*Campylobacter*	*Giardia*
Calicivirus	*Salmonella*	*Entamoeba histolytica*
Astrovirus	*E. coli*	*Cryptosporidium*
Parvovirus	*Shigella*	*Isospora belli*
Pestivirus	*Vibrio cholera*	*Strongyloides*
Adenovirus	*Aeromonas hydrophilia*	*Trichuris trichuria*
	Yersinia entercolitica	*Balantidium coli*
	Clostridium difficile	

Courtesy of Gilger [120]

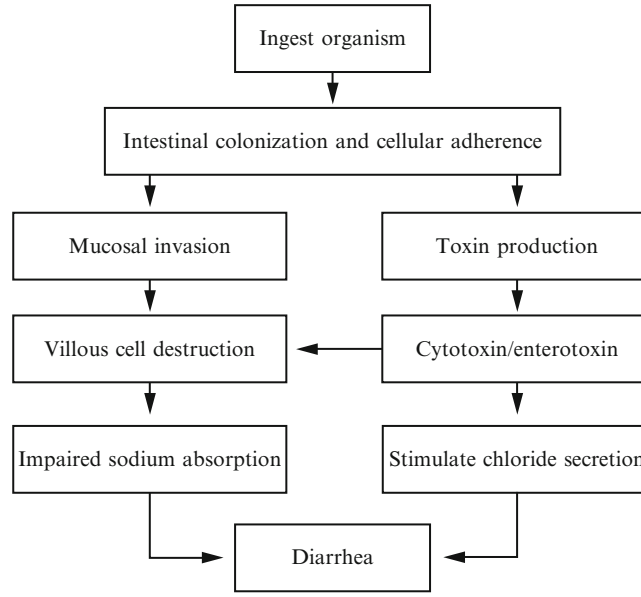

Fig. 10.1 The pathogenesis of acute infectious diarrhea (Courtesy of Gilger [120])

The pathophysiologic effects of diarrhea can be divided based on its effect on water absorption in the intestines. The common types are osmotic, secretory, motility, and inflammatory, although there is much overlap [5, 6]. Figure 10.1 describes the algorithm associated with the pathogenesis of acute infectious diarrhea.

Osmotic diarrhea results when solutes such as lactose are not absorbed properly. The higher than normal concentration of solutes in the lumen of the intestine pulls water into the lumen resulting in watery diarrhea. Rotavirus and *Shigella* both cause this type of diarrhea. Rotavirus selectively invades mature enterocytes and Shigella's toxin causes villous cell disruption leading to malabsorption. Secretory diarrhea is a result of the active secretion of water into the gut lumen. Certain substances (laxatives, bile acids, and fatty acids), infectious agents (*Clostridia*, *E. coli*, and *Staphylococcus aureus*), viral toxins, and certain congenital disorders (congenital chloride diarrhea) produce secretary diarrhea. Motility disorders, causing either hyper- or hypomotility can cause malabsorption and diarrhea, such as seen with irritable colon of infancy. Finally, inflammation of the intestine can cause either acute or chronic diarrhea. The resultant exudation of protein, blood, and mucus in the intestinal wall may lead to electrolyte and water loss either through the production of an enterotoxin or mucosal invasion [5, 6].

Diarrhea as defined by the World Health Organization (WHO) is the passage of three or more loose or watery stools per day with chronic diarrhea defined as stool volume of more than 10 g/kg/day in infants and toddlers, or more than 200 g/day in older children for more than 14 days [7]. Table 10.2 lists different etiologies of diarrhea based on the age of the patient. Dysentery is a general term used to describe a variety of intestinal inflammatory disorders marked by abdominal pain, tenesmus (straining with stool), and watery diarrhea containing blood and mucous. Although dysentery is most common in developing nations and people who are traveling to developing worlds (such as military personnel), certain people in developed nations are at increased risk of developing dysentery, including children in day care, people in nursing homes, and men who have sex with other men [3, 8]. For practical purposes, the clinical presentation of diarrhea can be classified as acute or chronic with purging (cholera and campylobacter) and hemorrhagic (Crohn's disease and ulcerative colitis) as subclasses.

Table 10.2 Etiology of diarrhea by age (Courtesy of Fleisher [121])

Cause	Infants and young children	Older children and adolescents
Gastrointestinal infections	Viruses	Viruses
	Bacteria	Bacteria
	Parasites	Parasites
Non-gastrointestinal infections (parenteral diarrhea)	Otitis media	Systemic infections
	Urinary tract infections	
	Other systemic infections	
Dietary disturbances	Overfeeding	Starvation stools
	Food allergy	
	Starvation stools	
Anatomic abnormalities	Intussusception	Appendicitis
	Hirschsprung's disease (a toxic megacolon)	Partial obstruction
	Partial obstruction	Blind loop syndrome
	Blind loop syndrome	
	Intestinal lymphangiectasis	
	Short bowel syndrome	
Inflammatory bowel disease		Ulcerative colitis (+/− a toxic megacolon)
		Crohn's disease (+/− a toxic megacolon)
Malabsorption or increased secretion	Cystic fibrosis	Celiac disease
	Celiac disease	Disaccharidase deficiency
	Disaccharidase deficiency	Acrodermatitis enteropathica
	Acrodermatitis enteropathica	Secretory neoplasms
Immunodeficiency	Severe combined immunodeficiencies and other genetic disorders	Human immunodeficiency virus
	Human immunodeficiency virus	
Endocrinopathy	Congenital adrenal hyperplasia	Hyperthyroidism
		Hypoparathyroidism
Miscellaneous	Antibiotic-associated diarrhea	Antibiotic-associated diarrhea
	Pseudomembranous colitis	Pseudomembranous colitis
	Toxins	Toxins
	Hemolytic uremic syndrome	Irritable bowel syndrome
	Neonatal drug withdrawal	Psychogenic disturbances

Evaluation

The priority in evaluating a child with diarrheal illness is to identify life-threatening conditions immediately so that appropriate referrals can be made. Several serious illnesses present with diarrhea including intussusceptions, hemolytic uremic syndrome (HUS), pseudomembranous colitis, appendicitis, toxic megacolon and congenital secretory, and osmotic diarrheas [9–13]. Next is to differentiate individuals in whom diarrhea is a secondary symptom such as those associated with otitis media, urinary tract infection, and pneumonia. In these children, the diarrhea is usually mild and self-limiting.

Because children behave differently than adults, it is important to keep in mind that they may present differently than adults. For example, infants have increased body surface area relative to weight and are more likely to develop fever causing increases in insensible water loss. They also have limited renal compensatory capacity and are more likely to become seriously ill and dehydrated during a diarrheal illness than an adult. In evaluating a child for hydration status, a systematic thorough approach must be implemented.

Laboratory Testing

Most children who present with acute diarrhea with minimal dehydration do not require further diagnostic testing. In children with significant isotonic volume depletion and toxic presentation, serum electrolytes should be tested as significant derangements may exist and must be corrected. An anion gap can be calculated from the serum electrolyte panel, which, if elevated, can be helpful in assessing the presence of a secondary underlying metabolic acidosis complicating the illness. There is conflicting evidence as to whether an elevated blood urea nitrogen (BUN) level is a reliable marker for assessing the degree of dehydration [14–16]. Most often, however, it is not necessary in patients with acute diarrhea, and studies have shown that there is no correlation found between BUN, anion gap, bicarbonate, or base excess/deficit and the total hospital length of stay [17]. If a blood gas is drawn, an arterial stick is the gold standard to give the best assessment of overall acid–base status. If this cannot be performed, a capillary blood gas can be done; however, peripheral venous sticks are not recommended, because they do not provide an accurate assessment of the patient's overall circulatory status. In a febrile child with frankly bloody or mucous-filled diarrhea, stool cultures should be obtained to identify a bacterial pathogen (identified in 15–20% of samples) [13, 18, 19]. A urine culture is indicated in a febrile female and in certain uncircumcised males, especially with a history of a urinary tract infection. Further imaging (ultrasound, air contrast enema, and computed tomography) is indicated whenever there is concern for intussusception, appendicitis, ovarian or testicular torsion, or other intra-abdominal processes, particularly in an ill appearing child [20]. There are commercially available assays to diagnose specific causes of GE, including rotavirus, calcivirus, astrovirus, and enteric adenovirus.

Diagnosis

A systematic approach to diagnosis is helpful in evaluating a child with diarrhea. The first critical step is an overall assessment of the child. Are they seriously ill appearing or not? Children with HUS or sepsis, as seen with *Salmonella*, may present with generalized toxicity or shock [13, 19, 21, 22]. Seizures may be the presenting symptom in children with severe shigellosis [23]. Of equal importance in the initial evaluation is to evaluate for signs of an acute abdominal process. Palpation of an abdominal mass or signs of peritonitis suggest intussusceptions, appendicitis, or possibly toxic megacolon. Prompt surgical referral can be lifesaving in these circumstances. Following the primary surveillance, the next step is ascertaining how long the diarrhea has persisted and whether or not it is accompanied by fever. Determine if the stool is bloody or non-bloody. It is imperative to identify children who are immunocompromised, as these children are at risk for unusual infections and require a more rigorous evaluation.

Many children presenting with non-bloody diarrhea and no fever history will have a viral enteritis, history of recent antibiotic use (typically amoxicillin), or signs consistent with overfeeding (an overweight child age 6–12 months with a history of excessive fluid intake) [24]. In an immunocompetent child with non-bloody diarrhea, the presence of fever is the trademark of infection [4]. Again, the majority of these children will have a viral etiology for their illness. Infectious enteritis typically manifests with fever and bloody or mucous-filled diarrhea. Psuedomembranous colitis must be considered if the child has a recent history of antibiotic exposure. Evaluation for amebiasis should be limited to endemic areas and to those who have recently traveled to such places. Rarely, a child with inflammatory bowel disease (IBD) will present with fever and bloody diarrhea and any child with a history of weight loss or recurrent abdominal pain should be further evaluated for IBD [25]. Of the most concern perhaps is the afebrile child who presents with bloody diarrhea. Life-threatening illnesses such as intussusception, pseudomembranous colitis, and HUS frequently present with afebrile bloody diarrhea. Prior to diagnosing the most common etiology, infectious enteritis, the aforementioned conditions must be excluded.

Viral Enteritis

Epidemiology/Incidence

In developed countries, approximately 2% of children born each year will be hospitalized by the time they reach 18 years of age for viral gastroenteritis [26, 28]. Children less than 5 years of age account for 95% of hospital admissions with the highest incidence in children between the ages of 3 months and 24 months [29]. In the USA over 200,000 children will be hospitalized for viral GE with 3–5 million visits to a health professional for a total of 15–25 million episodes per year [28, 36, 37]. Prior to the development and widespread distribution of the oral, live, tetravalent, rhesus-based rotavirus vaccine in 1998, rotavirus accounted for 50% of admissions to the hospital for nonbacterial GE in the USA [37–39]. Another 5–15% of admissions were for calciviruses, astroviruses, and enteric adenoviruses with up to 45% of cases attributed to an unidentified virus. Winter is the peak season for illness with 70–90% of the cases occurring during this time; however, some viruses are more predominant in certain seasons of the year (Table 10.3) [32, 38, 39].

Pathogenesis

Rotavirus is a part of the Reoviridae family with groups A and B causing the majority of illness in the USA [42]. It is typically transmitted via the fecal–oral route; however, contact and respiratory spread has been suggested. Incubation period is 24–72 h and the period of communicability is commonly 8 days, although in the immunocompromised patient the virus may be shed for 30 days or more [40]. The symptoms usually last for 4–6 days and children between the ages of 6 and 24 months are the most susceptible. Once the virus makes its way into the intestinal tract, it enters the villous epithelium of the jejunum and ileum and infects the enterocytes [41]. This damage to the wall of the small intestines leads to a transudation of fluid and net salt and fluid loss along with the inability to digest and absorb food leading to transient lactose intolerance. Further, secretory diarrhea has been postulated to involve alterations in intracellular Ca^{2+} mobilization within the intestinal lumen rendering it more susceptible to fluid secretion and resistant to fluid absorption [42].

Caliciviruses are small structured RNA viruses including the Norwalk-like virus or norovirus. They are responsible for the majority of outbreaks across all ages and are transmitted via the fecal oral route with suggestions of food, water, and shellfish as modes of transportation. Noroviruses were identified as the etiologic agent for half of the outbreaks of dysentery on cruise ships reported to the CDC in 2002. Incubation is 24–48 h with a period of communicability during the acute stage of 48 h [42–45].

Table 10.3 Differentiating features among viral causes of gastroenteritis (Courtesy of Matson [122])

Viruses	Predominant season	Age	Duration, days	Lactose intolerance	Common modes of transmission in order of frequency
Rotaviruses	Fall/Winter	6–24 months	5–7	Yes	Fecal–oral; respiratory?
Caliciviruses	All year (winter)	All ages	1–4	No	Fecal–oral, water; shellfish, foods, respiratory?
Astroviruses	Winter	All ages	3	Yes	Fecal–oral, water
Enteric adenoviruses	Summer	Children	6–9	Yes	Fecal–oral

Manifestation

The compilation of diarrhea, vomiting, fever, anorexia, headache, abdominal cramps, and myalgia are typical in rotavirus GE [42]. Stools may be watery or loose without blood or mucous, odorless or foul smelling, fecal leukocyte negative, pH <6, normal or pale in color with the presence of reducing substances. As many as 20 episodes of vomiting and or diarrhea can occur in any single day and severe isotonic dehydration can rapidly result, especially in young febrile children.

Caliciviral illness typically presents with more significant vomiting and, along with astrovirus and enteric adenovirus, is of shorter duration than rotavirus infection [42–45]. Diarrhea that persists for more than 5 days is more closely associated with enteric adenovirus infection [42]. Large common source outbreaks in children older than 2 years are most likely to be caused by caliciviruses and astroviruses [42–45].

Diagnosis

Diagnosis of viral GE is based on clinical presentation, age of patients, quantity and quality of stool and associated symptoms. Rarely are more comprehensive tests indicated. In an immunocompromised host, stool cultures for ova and parasites may be necessary to exclude parasitic or bacterial etiology. In the case of large outbreaks or in the hospitalized child with the intent of isolation cohorting, viral assays may be sent for specific agents or a broad reactive assay. Widely available assays such as the enzyme immunoassays (EIAs) and latex agglutination will detect rotaviruses and adenoviruses 40 and 41; however, the reverse transcription–polymerase chain reaction (RT–PCR) is required to detect astroviruses and norovirus caliciviruses [42–45].

Bacterial Enteritis

The differentiation of bacterial illness from viral illness may be difficult. In general, acute diarrheal illness with bloody or mucous-filled stools along with persistent high fevers is more common in bacterial illness than viral. Proven pathogens include *Campylobacter, Salmonella, E. coli, Shigella, Vibrio cholera*, *Aeromonas hydrophila*, *Yersinia enterocolitica*, and *C. difficile* [42].

Campylobacter

Epidemiology/Incidence

Campylobacter is one of the most common causes of bacterial gastroenteritis worldwide and, at its peak in 1996, was more common than *Salmonella* and *Shigella* infections combined. Improvements in food handling, especially of poultry, have caused a 26% decline in the incidence of infection with an average yearly infection rate of 2.4 million cases in the USA. Children less than 1 year of age and young adults aged 15–44 years are the most susceptible with an unexplained predominance in males. The vast majority of cases are linked to contaminated poultry (1 drop of chicken juice may contain 500 organisms); [42] however, infection has been linked to tainted unpasteurized milk, sausage, red meat, water, and contact with infected pets (especially birds and cats) [42–44, 46, 47].

Pathogenesis

Campylobacter species is a motile gram-negative bacilli of which there are over 14 species with *Campylobacter jejuni* being responsible for >99% of reported cases in the USA [42–46]. The organism spirals into the intestinal wall producing heat-labile enterotoxins which causes epithelial cell damage leading to secretory diarrhea. In the colon, diffuse inflammatory changes may be seen on sigmoidoscopy which mimic early IBD. Proliferation of the organism in mesenteric lymph nodes and the lamina propria following translocation may lead to additional infections such as meningitis, cholecystitis, urinary tract infection, and mesenteric adenitis [48].

Manifestation

Infected individuals present similarly to those with other bacterial causes of gastroenteritis, with symptoms including acute onset fever, abdominal cramps, and diarrhea. The diarrhea is either loose and watery or grossly bloody with leukocytes and blood detected in 75% of stool samples, and may be as frequent as ten stools a day at its peak [42, 46, 48]. The fever associated with campylobacter gastroenteritis may be low grade or >40 °C and typically lasts for 1 week and occurs in >90% of patients. Although the illness is usually self-limited, rare complications have been reported. Guillain–Barré syndrome (GBS) is the most common complication following infection and has been reported in 30% of cases with campylobacter identified as the proceeding illness. The risk of GBS is <1% following infection and severity of illness has no bearing on the risk of developing GBS [47]. If GBS does develop following *C. jejuni* infection, the morbidity of GBS (risk of irreversible neurological damage and need for mechanical ventilation) is greater [42, 47]. Other rare, post-infectious complications include reactive arthritis, uveitis, encephalopathy, carditis, HUS, and hemolytic anemia [42, 46, 48].

Diagnosis

The diagnosis of *C. jejuni* is by stool culture. The organism is difficult to grow due to its cephalothin resistance and can take up to 96 h for primary isolation. Species specific PCR-enzyme-linked immunosorbent assay may yield a higher detection rate of *C. jejuni* [42].

Salmonella

Epidemiology/Incidence

Approximately 1.4 million people acquire nontyphoid *Salmonella* infection in the USA each year. Most patients are younger than 20 with the highest rate of infection occurring in the summer and fall [42–44, 49, 50, 52]. The vast majority of cases are food-borne with less than 5% from direct contact with animal carriers (typically from reptile and amphibian sources) [50, 52, 53]. The most common sources are from poultry and eggs but fruit, vegetables, water, and milk are also common sources and most recently peanut butter and dry dog food have caused multi-state outbreaks [54].

Pathogenesis

Depending on the serotype of the *Salmonella* organism (a gram-negative facultative intracellular anaerobe), a broad spectrum of illnesses may result ranging from gastroenteritis, bacteremia, and focal infections to enteric fever such as those caused by the typhoid and paratyphoid serotypes [49, 50, 52, 54]. *Salmonella* is a member of the *Salmonella enterica* species, and there are over 2,500 serotypes which almost exclusively infect humans [55]. Once in the small intestine the organism colonizes and translocates across the intestinal epithelium. An inflammatory response mediated by cytokines, chemokines, neutrophils, macrophages, dendritic cells, and T and B cells ensues resulting in diarrheal illness. Replication occurs in mesenteric lymph nodes, the spleen and in macrophages in what is termed "Peyer's patches," and can disseminate to other organs (lungs, kidneys, gallbladder) or to the central nervous system [53].

Manifestation

Salmonella may present with gastroenteritis, enteric (typhoid) fever, bacteremia, or a localized infection. Gastroenteritis follows an incubation period of 8–48 h after the ingestion of a contaminated source and manifests as sudden onset fever, chills, nausea, vomiting, abdominal cramping, and diarrhea [44, 49, 51, 53]. Fever usually subsides within 72 h and the diarrhea may be grossly bloody lasting 3–7 days. Typhoid fever usually has an incubation period of 5–21 days and begins with 7–10 days of headache, cough, diaphoresis, anorexia, malaise, sore throat, and abdominal pain with "pea soup" diarrhea or constipation. Fever peaks in the second week of illness followed by splenomegaly, abdominal distension, abdominal pain, bradycardia, rash, meningismus, and/or mental confusion [51, 55]. If left untreated, individuals will either recover by the fourth week or go on to develop complications such as perforation (up to 10%), pneumonitis, pericarditis, orchitis, endocarditis, or focal abscesses. Bacteremia from *Salmonella* is rare in immunocompetent hosts and can lead to localized infection in as many as 10% of individuals. Localized infections can occur in nearly all human tissues including the endocardium, soft tissues, arteries, bones, joints, and the central nervous system [55].

Diagnosis

Stool cultures in people with gastroenteritis or severe diarrhea are most commonly positive for campylobacter and *Salmonella* [56].

Escherichia coli

Epidemiology/Incidence

Diarrheal illness caused by *E. coli* can be classified as either enterohemorrhagic, enterotoxigenic, enteroinvasive, enteropathogenic, enteroaggregative, or diffuse adherent [42]. Each type of infection is caused by different O-H serotypes and thus have differing clinical syndromes, pathogenesis, and possess distinct virulence properties. *Enterohemorrhagic E. coli* (EHEC) is common in developed countries and has a relatively long incubation period of up to 8 days with a period of communicability

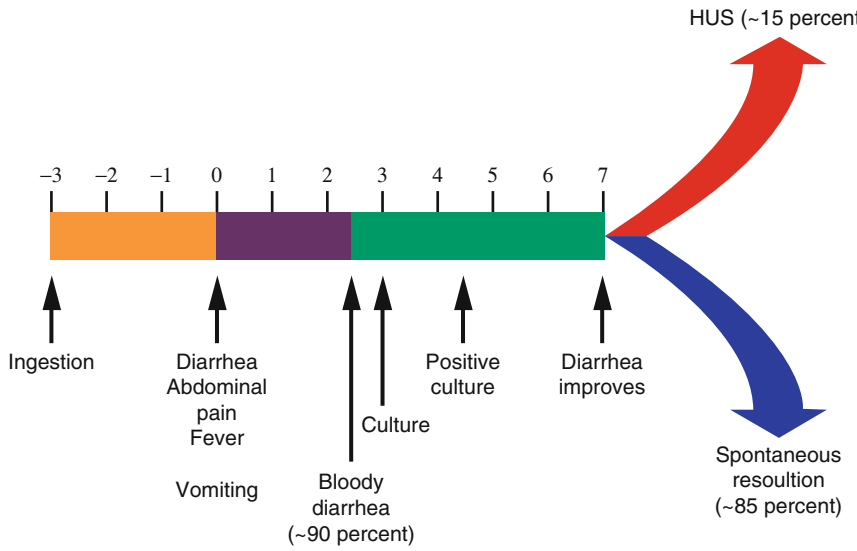

Fig. 10.2 Progression of *E. coli* O157:H7 infections in children. *HUS* hemolytic uremic syndrome (Reproduced with permission from Tarr et al. [125], Copyright © 2005 Elsevier)

as long as 3 weeks in some children. Cattle are the most recognized reservoir followed by humans and deer. Outbreaks have been attributed to undercooked hamburger meat, unpasteurized milk, apple cider, and alfalfa sprouts [42, 43]. *Enterotoxigenic* strains of *E. coli* are more common in developing countries and in travelers to these less industrialized countries. The incubation period is much shorter than the other strains of *E. coli* infection, ranging from 10 to 72 h with humans as the major reservoir. The period of communicability lasts as long as the excretion of the pathogen lasts, which can be prolonged. Transmission is through contaminated food and water. *Enteroinvasive E. coli* is endemic in developing countries with occasional outbreaks reported in more industrialized nations. The incubation period is 10–18 h with a period of communicability lasting the duration of excretion of the organism. Humans serve as the reservoir and it has been suggested that contaminated food serves as the mode of transmission. *Enteroaggregative E. coli* is an important form of infantile diarrhea in Latin America, Asia, and the Democratic Republic of Congo and has occasionally been reported in Europe. The incubation period is between 20 and 48 h. *Diffuse-adherence E. coli* is the least understood of the strains of *E. coli* diarrhea. It is thought to be more common in preschool children rather than infants or toddlers, but little is known in regards to incubation, transmission, and manifestation [42, 43].

Pathogenesis

E. coli are gram-negative bacteria that commonly live harmoniously in the intestinal tract of humans and animals. They can survive with or without air and comprise over 700 serotypes. The five forms of pathogenic serotypes attach to the intestinal wall and produce harmful toxins which cause inflammation and diarrhea.

EHEC diarrhea is caused by the serotype *E. coli* O157:H7, which produce potent cytotoxins Shiga 1 and Shiga 2 [42, 43]. Figure 10.2 demonstrates the progression of *E. coli* O157:H7 infections in children.

Manifestation

E. coli O157:H7 causes diarrhea that ranges from mild and non-bloody to stools that are nearly all blood without fecal leukocytes [42, 43]. The most serious morbidity of this infection is the development of HUS and thrombotic thrombocytopenic purpura [42, 43, 57–60]. Fortunately, only 2–7% of individuals with EHEC diarrhea will develop HUS. *Enterotoxigenic E. coli* diarrhea manifests similar to *Vibrio* with profuse watery diarrhea without blood or mucus, abdominal cramps, vomiting, dehydration, prostration. and acidosis and may or may not present with low grade fevers [42, 43]. *Enteroinvasive* strains most closely resemble *Shigella* presenting with severe abdominal cramps, malaise, watery diarrhea, tenesmus, and fever. In a few individuals (<10%), the illness will progress to the passage of multiple, scanty, fluid-filled stools containing blood and mucous which is leukocyte positive [42, 43]. *Enteroaggregative E. coli* produces chronic watery diarrhea with mucous in infants and young children.

Shigella

Epidemiology/Incidence

The incidence and epidemiology of *Shigella* varies greatly according to the specific strain and serotype. The CDC estimates the overall incidence of shigellosis in the USA to be around 450,000 cases a year [62]. The peak season is during the summer months and it most commonly affects children younger than 5 years of age. The natural reservoir is humans and primates. The mode of transmission is via contaminated food and water sources by means of the fecal oral route. The infectivity load is extremely small and insects such as flies can serve as vectors carrying contaminated fecal matter from one place to another. The incubation period is 12 h to 7 days (mean 2–4 days) and the period of communicability can be as long as 4 weeks.

Pathogenesis

Shigella are nonmotile, nonencapsulated gram-negative bacteria. There are four strains, each with several serotypes. *Shigella* produces two major groups of enterotoxins: Stx1 and Stx2. These enterotoxins adhere to the intestinal wall and increase inflammatory cytokine production in macrophages, increasing interleukin (IL)-8, and damage the colonic mucosa. When the enterotoxins adhere to the small-intestinal wall, they act by blocking the absorption of electrolytes, glucose, and amino acids. Subunits of the enterotoxins inhibit protein synthesis causing cellular death, macrovascular damage to the intestine, apoptosis in renal tubular epithelial cells, and hemorrhage [63, 64].

Manifestation

The signs and symptoms of shigellosis are dependent on the serotype and include sudden onset high fevers, severe abdominal cramping, emesis, anorexia, and large volume watery diarrhea. Following the initial manifestations, individuals may develop tenesmus, urgency, abdominal cramps, and frequent small volume mucous-filled stools with frank blood. Septicemia and chronic diarrhea are common. According to the degree of dehydration, children may exhibit tachycardia and tachypnea

with dry mucous membranes, electrolyte disturbances, and generally appear toxic [63–65]. *Shigella* may manifest in distant organs such as the renal glomerural and tubular epithelia producing microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. Seizures may be an early manifestation including headaches, lethargy, meningismus, and delirium. The etiology of extraintestinal CNS manifestations is poorly understood but not thought to be caused by enterotoxin [61]. Complications of shigellosis include rectal prolapse, toxic megacolon, HUS, and Reiter syndrome (a form of reactive arthritis that effects about 2% of individuals) [62–65].

Diagnosis/Treatment

Isolation of the *Shigella* organism from feces or rectal swab specimens is diagnostic. Testing the feces as soon as the specimen is received improves sensitivity. Rapid membrane (dot) ELISA tests recently made available have demonstrated improved diagnostic accuracy and reduced turn around time which is imperative when considering the high epidemic potential and severe morbidity of type I *Shigella dysenteriae*.

Toxic infection requires antibiotic treatment. Unfortunately, several serotypes have developed drug resistance and it is imperative that sensitivities are performed to guide treatment. Common antibiotic regimens include ampicillin, trimethoprim/sulfamethoxazole, ceftriaxone, or ciprofloxacin. Antidiarrheal agents such as Lomotil (diphenoxylate with atropine) and Imodium (loperamide) should be avoided as they can make the infection worse by slowing the shedding of the toxins.

Vibrio cholera

Epidemiology/Incidence

V. cholera has long been recognized as a cause of diarrheal illness in Asia and Latin America. More recently, there have been reports of endemic toxigenic *V. cholera* in parts of the USA such as the Gulf coast of Louisiana and Texas [67]. Following Hurricane Katrina in 2005, the CDC reported 22 new cases of *Vibrio* infection, likely related to the disturbance in the environment [68]. Although *Vibrio* is not a compulsory reportable infection (as it is considered a food borne illness), it is estimated that between 1996 and 2004 the incidence of *Vibrio* infections increased 47%, whereas the incidence of Shiga toxin-producing *E. coli* O157:H7 and species of *campylobacter*, *Listeria*, *Salmonella*, and *Yersinia* significantly decreased during this same time span [43]. Humans are the only known host but the organism can live freely in an aquatic environment such as the Gulf of Mexico, New England, and the northern pacific. The typical mode of transmission is the ingestion of contaminated water or food (particularly raw or under cooked shellfish) [69]. Moist grains and vegetables held at ambient temperature have also been implicated as a source of infection. The incubation period ranges from a few hours to 5 days, but is typically 1–3 days. Although other food borne bacterial infections such as *Campylobacter*, *Listeria*, and *Salmonella* are much more common than *Vibrio* infections, the mortality rate associated with *Vibrio* infections (39%) is much higher due to the incidence of *V. vulnificus* septicemia [70–72]. *Vibrio* infections have no predilection for race, sex, or age.

Pathogenesis

V. cholera belongs to the vibrionaceae family and is a gram-negative, oxidase-positive, curved, motile bacilli with several serotypes; however, only serotypes O1 and O139 are known to cause

epidemic cholera [67]. In the USA, *Noncholera vibrio* species are becoming more common. *Vibrio parahaemolyticus* is the most common and *Vibrio vulnificus* is the most deadly [69, 73, 74]. The *Vibrio* organism is capable of producing multiple extracellular cytotoxins and enzymes which are able to inflict extensive tissue damage.

Manifestation

V. cholera characteristically presents with painless, voluminous, watery diarrhea which is colorless with small flecks of mucous and contains large amounts of sodium, potassium, chloride, and bicarbonate. It is classically described as "rice-water" diarrhea. Abdominal cramps and fever are not typically reported. Dehydration, metabolic acidosis, and shock may result if fluid losses are not replaced promptly. *Noncholera vibrio* infections can manifest as gastroenteritis, septicemia, or wound infections with no reliable characteristic signs and symptoms. *Vibrio* gastroenteritis may present with low grade fevers, nausea, vomiting, abdominal cramping, and diarrhea. Up to 75% of individuals infected with *V. fluvialis* demonstrate bloody diarrhea, whereas only 25% infected with *V. parahamolyticus* develop bloody diarrhea [75]. *Noncholera vibrio* septicemia manifests with high fevers, chills, myalgia, exquisite lower extremity pain, and edema. Extensive ecchymosis and multiple hemorrhagic bullae can develop on the lower extremities and hypovolemic shock, unresponsive to aggressive intravenous rehydration efforts, may develop within 24 h followed by multi-organ failure.

Diagnosis/Treatment

The selective medium thiosulfate–citrate–bile salts–sucrose stool culture has the highest sensitivity for identifying *Vibrio* infection. When testing stool or emesis, it is essential to request specific testing for *Vibrio* species and sensitivities, as drug resistance is not uncommon. In addition to culture testing, depending on systemic illness, blood chemistries, DIC panel, and blood gas analysis may be indicated.

Treatment focuses on rehydration therapy and symptomatic support. Specific antimicrobial therapy for cholera includes treatment with oral doxycycline or tetracycline. Resistant strains have been treated with ciprofloxacin and trimethoprim-sulfamethoxazole. *Noncholera vibrio* infections have been treated with ceftazidime, doxycycline, ticarcillin, clavulanate, piperacillin, and tazobactam. Adjuvant therapy such as recombinant human activated protein C (drotrecogin alfa activated) has been used in patients with severe sepsis [77].

Yersinia enterocolitica

Epidemiology/Incidence

In many countries, *Y. enterocolitica* has eclipsed *Shigella* as the predominate cause of gastroenteritis in young children and has rivaled *Salmonella* and *Campylobacter* species [67, 69, 78]. Pigs are the major animal reservoir for *Y. enterocolitica* strains that are pathogenic to humans, however, other strains are also found in many other animals including rodents, rabbits, sheep, cattle, horses, dogs, and cats. The incubation period is 4–7 days. The mode of transmission is via blood transfusion or via the ingestion of contaminated food and liquids such as pork, milk, water, and tofu. The period of communicability is lengthy and shedding of the organisms in the stool has been detected up to 90 days following symptom resolution [78, 79].

Pathogenesis

Y. enterocolitica belongs to a group of non-lactose fermenting gram-negative bacilli including *Yersinia pseudotuberculosis*, which are glucose fermenting and oxidase negative. In the USA, most human illness is caused by one species, *Y. enterocolitica*. Although not fully understood, it is postulated that the *Y. enterocolitica* species causes tissue destruction by means of either chromosomally mediated effects or plasmin-mediated effects. It is known that the bacteria colonize and produce disease in the small intestine which leads to the colonization of underlying lymphoid tissues described as Peyer's patches. From colonization within these patches, the organism can disseminate to extra-intestinal sites. Following the incubation period, infection can result in mucosal ulceration and perforation, necrosis at the site of the Peyer's patches, and mesenteric lymph node enlargement [80, 81].

Manifestation

Presenting signs and symptoms of *Y. enterocolitica* infection are varied depending on the age of the person infected. Symptoms typically develop 4–7 days after exposure and, in children, fever, vomiting, abdominal pain, and bloody diarrhea are common. In older children and adults, manifestations include enterocolitis, septicemia, pharyngitis, dermatitis, myocarditis, pseudoappendicitis, mesenteric adenitis, reactive arthritis, erythema nodosum, and glomerulonephritis [82–84]. Because *Y. enterocolitica* requires iron for growth, individuals with iron overload (hereditary hemochromatosis and chronic hemolysis) are at increased risk of developing severe systemic infection.

Diagnosis/Treatment

Distinguishing *Y. enterocolitica* from other invasive pathogens in routine stool samples may be difficult. Isolation of *Y enterocolitica* from otherwise sterile samples, such as blood, CSF, and lymph node tissue, is usually faster than recovery from stool samples.

As with other bacterial infections, treatment is aimed at maintaining hydration and at symptomatic relief. In cases of severe systemic illness, treatment with aminoglycosides, chloramphenicol, tetracycline, trimethoprim-sulfamethoxazole, piperacillin, ciprofloxacin, and third-generation cephalosporins have been shown to shorten the course of illness.

Clostridium difficile

Epidemiology/Incidence

C. difficile is present in the intestinal flora of as many as 2–3% of healthy adults and as many as 70% of infants [85] Outbreaks of *C. difficile* diarrhea typically occur in hospitals or outpatient treatment centers where the spores are present. It is responsible for as many as three million cases of diarrheal illness and colitis per year. The incidence of infection in hospitalized individuals has steadily been increasing from 30 to 40/100,000 in the 1990s to 84/100,000 in 2005. It has been reported that 20% of hospitalized individuals will acquire *C. difficile* at one point in their hospitalization and that 30% of these patients will develop diarrheal illness making *C. difficile* the most prevalent nosocomial infection [85–88]. The incubation period is unknown but patients can present within hours of exposure or not for months following antibiotic use. The mode of transmission is via the fecal oral route presumed to be from care workers

soiled hands or contaminated environment. The greatest risk is for those who receive antibiotic therapy, especially broad-spectrum antibiotics or antibiotic treatment of long duration.

Pathogenesis

C. difficile are gram-positive anaerobic spore forming bacilli. They are capable of surviving in the environment for several months to a year by forming a heat resistant spore. Once they find their way into the intestinal tract of a healthy host, the normal gut flora is capable of resisting overgrowth and colonization. When the normal gut flora is disrupted, as with exposure to antibiotics, *C. difficile* evades immune responses, proliferates in the colon, and produces toxins. The two distinct toxins that are produced by pathogenic strains of *C. difficile* are Toxin A, which is an enterotoxin, and toxin B, which is a cytotoxin. These two toxins work together to bind with specific receptors in the intestinal wall, where they stimulate the production of tumor necrosis factor-alpha and proinflammatory interleukins which contribute to the inflammatory response and formation of an adherent yellow appearing plaque in the intestinal mucosa termed a pseudomembrane. The disruption in the colonic wall increases permeability resulting in watery diarrhea. In rare circumstances, the damage can be so extensive as to lead to perforation, peritonitis, or toxic megacolon.

Manifestation

Most individuals present with mild to moderate watery diarrhea (rarely bloody), cramping abdominal pain, anorexia, malaise, and fever during or shortly after starting a course of antibiotics. However, up to 40% may not develop symptoms for as many as 10 weeks following antibiotic exposure [86]. The most common antibiotics implicated in the development of *C. difficile* diarrhea include the cephalosporins (especially second and third generation), ampicillin/amoxicillin, and clindamycin. Agents occasionally attributed to the development are the macrolides and other penicillins.

Diagnosis/Treatment

Any hospitalized individual who develops diarrhea following antibiotic exposure should have a stool sample sent to detect *C. difficile* toxins. Typical studies include an EIA, PCR, or tissue culture assay. When evaluating for fulminant disease or pseudomembrane, a flexible colonoscopy or CT scan may be helpful. Cessation of the causative antibiotics may be the only treatment necessary in mild cases and should be attempted whenever possible. In moderate cases, oral treatment with metronidazole or vancomycin is effective. In fulminant disease, a combination of intravenous metronidazole and oral vancomycin may be required. Patients are expected to show improvement within 4 days; however, the relapse rate is relatively high with as many as 27% of individuals suffering a relapse within 3 weeks following the cessation of therapy [86, 87]. The reason for the high reoccurrence rate is not fully understood but is thought to be a result of failure to eradicate the organism from the colon, or from a subsequent re-exposure from within the environment. Unproven adjunct therapies on the horizon include the use of probiotics to hasten recolonization of normal gut flora, nitazoxanide in lieu of metronidazole, rifaximin to prevent relapse following treatment with vancomycin, cholestyramine to bind *C. difficile* toxins A and B (also binds vancomycin so it cannot be used concurrently with oral vancomycin), and intravenous immune globulin for refractory disease in those individuals felt to have a poor immune response. Antidiarrheal agents must not be utilized as these may increase the severity and duration of illness [85–88].

Parasitic Infection

Giardia is the most common human parasitic disease in the USA. It infects around 2% of adults and 6–8% of children in developed countries worldwide and up to 33% of people living in less industrialized nations have had giardiasis at some point in their lives [89]. Although anyone can get giardiasis, those at increased risk are travelers to countries where giardiasis is common, backpackers or campers who drink untreated water, and people exposed to infected animals or other humans. *Giardia* (termed *Giardia intestinalis*, *Giardia lamblia*, or *Giardia duodenalis*) is a microscopic protozoan flagellate which is protected by an outer shell which allows it to live outside of a host for long periods of time even in extreme temperatures and renders it resistant to standard disinfectants such as chlorine. The cysts are found in the soil, food, and water that has been contaminated with feces from infected humans or animals. Ingestion of as little as ten cysts may cause illness and an infected individual can shed 1–10 billion cysts daily in their feces [90]. Shedding of the parasite can persist for several months. Infection occurs following ingestion of cysts in the small intestine where excystation causes the release of trophozoites which then multiply and attach to the mucosa by a ventral sucking disk. The presenting signs and symptoms vary and can last for 1–2 weeks or longer. Typical acute symptoms include diarrhea with greasy stools that tend to float, flatulence, abdominal cramping, nausea, vomiting, and dehydration. Some individuals will remain asymptomatic and in others the symptoms may wax and wane over a period of a few days to weeks. In more extreme cases and in those not treated, *Giardiasis* can cause weight loss and failure to absorb fat, lactose, vitamin A, and vitamin B12. Diagnosis is by fecal immunoassays. The testing of three stool specimens collected every other day increases test sensitivity. Treatment with metronidazole, tinidazole, or nitazoxanide is typically effective [90–92].

Cryptosporidiosis is another common parasitic infection known to cause diarrheal illness worldwide. It is estimated that 748,000 cases of cryptosporidiosis occur annually in the USA alone. Several outbreaks of cryptosporidium have occurred in American water parks, community swimming pools, and day care centers. There are many species of *Cryptosporidium* that are pathogenic to humans and a wide range of animals. C*ryptosporidium parvum* and *Cryptosporidium hominis* (formerly known as *C. parvum* anthroponotic genotype or genotype 1) are the most prevalent species causing disease in humans. Like giardia, *Cryptosporidium* are microscopic parasites found in contaminated water and spread by fecal oral transmission. They are encapsulated like the giardia spores and can survive outside a host for long periods and are similarly resistant to chlorine. Following ingestion of the sporulated oocysts, excystation occurs releasing the sporozoites which then attach to the hosts intestinal epithelial cells and those of the respiratory tract. The parasites then multiply, producing two different types of oocysts, one which is commonly excreted from the host, and the other which is primarily involved in autoinfection. Symptoms of cryptosporidiosis generally begin around 7 days (ranging 2–10 days) after becoming infected with the parasite. Although some infected people will be asymptomatic, the most common symptom of cryptosporidiosis is watery diarrhea. Other symptoms include abdominal cramping, dehydration, nausea, vomiting, fever, and anorexia. Symptoms usually last about 1–2 weeks in healthy individual and resolve spontaneously. Like giardia, people may experience symptoms which can come and go for up to 30 days. Immunocompromised individuals may develop serious, chronic, and sometimes fatal illness. Diagnosis is based on history and stool specimens which are examined microscopically with acid-fast staining, direct fluorescent antibody, and/or EIAs for detection of *Cryptosporidium* sp. antigens. Several stool samples may be required to increase sensitivity. Treatment is supportive and rarely requires aggressive intervention. In those with severe disease, nitazoxanide is the treatment of choice. The most common symptom of *Cryptosporiosis* is watery diarrhea and the antibiotic of choice is trimethoprim-sulfamethoxazole [93, 94].

Entamoeba histolytica is another microscopic parasite which commonly affects people living in the tropics and in areas with poor sanitary conditions. Only about 10–20% of people who are infected

with *E. histolytica* become sick from the infection. Symptoms typically develop within 2–4 weeks of exposure, though it can sometimes take longer. Rarely, it can cause amebic dysentery associated with stomach pain, bloody diarrhea, and fever. If *E. histolytica* invades the liver, it can form an abscess and there are reports in a small number of instances, where it has spread to other parts of the body, such as the lungs or brain, but this is very uncommon. Diagnosis of amebiasis can be very difficult as several parasites resemble *E. histolytica* on microscopic exam and like the other parasitic infections it may take several stool samples to yield a positive result. Luminal amoebicides (such as paromomycin, diloxanide furoate, and iodoquinol) and metronidazole are effective treatments [95].

Strongyloides stercoralis (nematode or roundworm) is a parasitic infection which infects approximately 30 million people worldwide and is endemic to tropical, subtropical, and temperate areas including the Appalachian region of the southern USA.

The filariform larvae in contaminated soil penetrate the human skin, and are transported to the lungs where they penetrate the alveolar spaces. From the alveolar spaces, they are carried through the bronchial tree to the pharynx where they are swallowed and travel to the small intestine where they initiate the parasitic cycle.

The females live threaded in the epithelium of the small intestine and by parthenogenesis produce eggs which yield rhabditiform larvae. These rhabditiform larvae can either be passed in the stool or can cause autoinfection. Most people infected with *Strongyloidoisis* are asymptomatic but immunocompromised individuals may develop disseminated disease. Common manifestations include abdominal pain and diarrhea. Pulmonary symptoms (including Loeffler's syndrome) can occur during pulmonary migration of the filariform larvae. Other symptoms include urticarial rashes in the buttocks and waist areas. In disseminated strongyloidiasis, which can be fatal, patients may present with acute abdominal pain, distension, shock, pulmonary and neurologic complications, and septicemia. Diagnosis is based on the presence of the parasite in stool samples. Duodenal fluid may be examined using techniques such as the Enterotest string or duodenal aspiration. Larvae may also be detected in sputum from patients with disseminated strongyloidiasis. Treatment options for uncomplicated disease include thiabendazole, ivermectin, and albendazole [96–98].

Trichuris trichuria (whipworm) is the third most common roundworm pathogenic to humans. It is a soil-transmitted helminth frequently found in areas with tropical weather and in the southern USA. Trichuriasis is transmitted by the fecal-oral route or through ingestion of feces contaminated food and often occurs in areas with poor sanitation and where human feces is used as fertilizer. An estimated 604–795 million people in the world are infected with whipworm. The whipworm lives in the large intestine of the host and eggs are passed in the feces, which, if ingested by another human, begins the parasitic cycle anew. People with Trichuriasis may be asymptomatic or may become very ill. Symptoms include the painful frequent passage of bloody or watery or mucous-filled stool. In severe cases, rectal prolapse has been reported. Diagnosis is by microscopic identification of the parasite in the stool and treatment is with albendazole and mebendazole [99].

These causes of chronic diarrhea overlap somewhat with the etiology of acute diarrhea and are beyond the scope of this chapter.

Treatment

There have been guidelines developed over the years from various societies to help standardize the treatment of AGE, particularly, in an outpatient setting. A study from 2010 showed that guidelines for the treatment of mild to moderate AGE are poorly applied by primary care physicians [100]. In order to properly treat AGE, the degree of dehydration must be assessed.

Degrees of Dehydration

A thorough and proper history and physical exam is the key to determining the degree of dehydration in a patient. In neonates, the anterior fontanelle may be soft and flat with minimal dehydration vs. sunken in severe dehydration, but this physical finding alone can be misleading without ensuring a complete evaluation of the child, including his mental status. Proper interpretation of vital signs is essential, and low blood pressure is a late sign of dehydration that must be treated aggressively with intravenous (IV) hydration. It may be difficult to assess the amount of urine output if it is mixed with diarrheal stools in infants and young children; however, if a urine sample can be obtained, a high specific gravity (≥1.020) can be an indication of dehydration [101]. Historically, dehydration is divided into three classes depending on the percent of fluid deficit: mild (3–5%), moderate (6–9%), and severe (≥10%, with signs of shock). Previous studies have found that the first clinical signs and symptoms of dehydration are not evident until the patient is at least 3–4% dehydrated, and it may be difficult to distinguish between mild and moderate dehydration on the basis of clinical signs alone [101, 102].

Tables 10.4 and 10.5 list the signs and symptoms associated with the degrees of dehydration, and the indications for referral for medical evaluation in children with acute diarrhea, as these are key to determining the route and type of therapy for the patient.

Table 10.4 Signs and symptoms of different degrees of dehydration (Courtesy of King et al. [2])

Symptom	Minimal or no dehydration (<3% loss of body weight)	Mild to moderate dehydration (3–9% loss of body weight)	Severe dehydration (>9% loss of body weight)
Mental status	Well; alert	Normal, fatigued or restless, irritable	Apathetic, lethargic, unconscious
Thirst	Drinks normally; might refuse liquids	Thirsty; eager to drink	Drinks poorly; unable to drink
Heart rate	Normal	Normal to increased	Tachycardia, with bradycardia in most severe cases
Quality of pulses	Normal	Normal to decreased	Weak, thready, or impalpable
Breathing	Normal	Normal; fast	Deep
Eyes	Normal	Slightly sunken	Deeply sunken
Tears	Present	Decreased	Absent
Mouth and tongue	Moist	Dry	Parched
Skin fold	Instant recoil	Recoil in <2 s	Recoil in >2 s
Capillary refill	Normal	Prolonged	Prolonged; minimal
Extremities	Warm	Cool	Cold; mottled; cyanotic
Urine output	Normal to decreased	Decreased	Minimal

Sources: Adapted from Duggan et al. [123], World Health Organization [124]

Table 10.5 Indications for referral for medical evaluation in children with acute diarrhea (Adapted from King et al. [2])

Young age (e.g., age <6 months or weight <8 kg)
History of premature birth, chronic medical conditions, or concurrent illness
Fever (>38 °C for infants <3 months or ≥39 °C for children 3–36 months)
Visible blood in stool
Frequent and substantial volumes of diarrhea
Persistent vomiting
Caregiver's report of signs consistent with dehydration (e.g., sunken eyes or decreased tears, dry mucous membranes, or decreased urine output)
Change in mental status (e.g., irritability, apathy, or lethargy)
Suboptimal response to oral rehydration therapy already administered
Inability of the caregiver to administer oral rehydration therapy

Table 10.6 Summary of therapy based on percent dehydration (Adapted from King et al. [2])

Degrees of dehydration	5%	5–10%	>10%
Rehydration	None	ORS: 50–100 mL/kg BW over 4 h	LR or NS: 20 mL/kg BW IV until improvement in perfusion and mental status is seen, followed by 100 mL/kg BW ORS over 4 h, or D1/2 NS IV running at twice maintenance if patient not able to tolerate oral intake
Fluid replacement	<10 kg BW: 60–120 mL ORS for each diarrheal stool or episode of emesis	Same as 5% dehydration	Same as 5% if able to tolerate fluids, NGT can be used for ORS replacement; D1/4 or D ½ NS + 20 mEq KCl/L IV
Nutrition	Maintain breast-feeding or regular diet for age, ensuring adequate caloric intake	Same as 5% dehydration following initial rehydration therapy	Same

ORS oral rehydration solution; mL/kg; *BW* milliliters per kilogram body weight; *IV* intravenous; *D* dextrose; *NS* normal saline; *LR* lactated ringers; *KCl* potassium chloride

A recent study from Italy evaluated the applicability and efficacy of guidelines for the management of AGE as used by pediatricians. Results showed that the duration of diarrhea was shorter in the group of patients treated by pediatricians who underwent training in AGE management than in those patients whose pediatricians who were not officially trained. The four major recommendations in the guidelines are as follows:

1. Rapid oral rehydration for 3–4 h with a hypoosmolar solution (Sodium 60 mmol/L)
2. Refeeding after 4 h of rehydration with the patient's normal diet, including solids, full-strength formula, or milk, with no restriction of lactose intake
3. Avoidance of unnecessary medications
4. Avoidance of microbiological investigations

This study found that many physicians do not follow these guidelines, with the prescription of an elimination diet (the temporary withdrawal of lactose) and the use of antidiarrheal medications (probiotics) as the two biggest violations of the guidelines [100].

In 2008, The European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases established evidence based guidelines for the management of AGE in children in Europe. They recommend that hospitalization should be reserved only for those patients in need of procedures such as intravenous rehydration. Otherwise, oral rehydration is the key treatment and should be applied as soon as possible with reduced osmolarity solution offered often.

There is again, emphasis placed on the administration of a regular diet to the patient, and the avoidance of antibiotics, except for when treating AGE secondary to Shigellosis and early stage *Campylobacter* infection [27].

Rehydration and Maintenance

Therapy for AGE should be tailored to the degree of dehydration present and should be done in two phases: rehydration and maintenance. Table 10.6 summarizes the approaches to therapy for the different degrees of dehydration. For patients with minimal or no dehydration from AGE, the goal is to

Table 10.7 Types of oral rehydration and electrolyte contents

Solution	Carbohydrate (gm/L)	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Base[a] (mmol/L)	Osmolarity (mOsm/L)
ORS						
World Health Organization (WHO) (2002)	13.5	75	20	65	30	245
WHO (1975)	20	90	20	80	30	311
European Society of Paediatric Gastroenterology, Hepatology and Nutrition	16	60	20	60	30	240
Enfalyte®[b]	30	50	25	45	34	200
Pedialyte®[c]	25	45	20	35	30	250
Rehydralyte®[d]	25	75	20	65	30	205
CeraLyte®[e]	40	50–90	20	NA[f]	30	220
Commonly used beverages (not appropriate for diarrhea treatment)						
Apple juice[g]	120	0.4	44	45	N/A	730
Coca-Cola®[h] Classic	112	1.6	N/A	N/A	13.4	650

[a]Actual or potential bicarbonate (e.g., lactate, citrate, or acetate)
[b]Mead-Johnson Laboratories, Princeton, NJ. Additional information is available at http://www.meadjohnson.com/products/cons-infant/enfalyte.html
[c]Ross Laboratories (Abbott Laboratories), Columbus, OH. Data regarding Flavored and Freezer Pop Pedialyte are identical. Additional information is available at http://www.pedialyte.com
[d]Ross Laboratories (Abbott Laboratories), Columbus, OH. Additional information is available at http://rpdcon40.ross.com/pn/PediatricProducts.NSF/web_Ross.com_XML_PediatricNutrition/96A5745B1183947385256A80007546E5?OpenDocument.
[e]Cera Products, LLC, Jessup, MD. Additional information is available at http://www.ceralyte.com/index.htm
[f]Not applicable
[g]Meeting US Department of Agriculture minimum requirements
[h]Coca-Cola Corporation, Atlanta, GA. Figures do not include electrolytes that might be present in local water used for bottling.
Base = phosphate
Courtesy of Centers for Disease Control and Prevention

provide adequate fluids while continuing an age-appropriate diet. If the mother is breast-feeding, this should continue even during the initial rehydration phases. In practice, 1 mL of fluid should be given for each gram of output; however, if losses cannot be measured (e.g., in an outpatient setting), 10 mL of additional fluid is given per kilogram (kg) body weight for each diarrheal stool or 2 mL/kg body weight for each episode of emesis. Further simplifying based on weight: if the patient is <10 kg, he should receive 60–120 mL (2–4 oz) of fluid for each episode of emesis or diarrhea that occurs. Patients with mild to moderate dehydration from AGE should have the estimated fluid deficit rapidly replaced using 50–100 mL of an oral rehydration solution (ORS) per kg body weight over 2–4 h. This should be followed by ongoing administration of ORS either by mouth or via a nasogastric (NG) tube if necessary, in vomiting patients. Rapid NG rehydration has been found to be well-tolerated, more cost-effective, and associated with fewer adverse effects than rapid IV rehydration [2, 102–104].

Table 10.7 lists the different ORS solutions available for rehydration and maintenance therapy, as well as common beverages which should not be used as treatment for diarrhea.

The WHO and United Nations Children's Fund (UNICEF) recommend a reduced osmolarity solution for global use after finding no clinical difference (except for nonsymptomatic hyponatremia), between patients treated with lower osmolarity ORS solution vs. those treated with the standard ORS solution. The biggest differences between the WHO-ORS solution and the common pedialyte solution used in the USA are the carbohydrate, sodium, and chloride contents, though either solution is adequate to treat AGE. It is more important to recognize that the commonly administered soft drinks or apple juice are extremely low in nutritional value and high in osmolarity, which could contribute to worsening symptoms of diarrhea in children and should, therefore, never be recommended as therapy [102].

Patients who are severely dehydrated demonstrating signs of hypovolemic shock (poor pulses, prolonged capillary refill, altered mental status) require immediate IV rehydration with normal saline (NS), Lactated Ringer's (LR), or a similar isotonic solution in a 20 mL/kg body weight dose.

Repeated doses of IV rehydration should be administered until symptoms of hypovolemic shock begin to improve, or until the patient can be admitted into the hospital for further monitoring.

Ideally, most patients with AGE and dehydration should be treated as an outpatient, with frequent follow up visits with the primary care physician to assess the hydration status throughout the illness. There are times, however, when despite the best home or outpatient management, the patient requires admission to the hospital for further care. Indications for hospital admission include the parents' inability to manage oral rehydration at home, usually because of the patient having inadequate intake from refusal or emesis, or worsening diarrhea resulting in severe dehydration. Younger patients can be more prone to severe dehydration; therefore, it is recommended that if a child is less than a year of age or if the diagnosis is not certain, closer observation in a hospital setting may be of benefit. Other risk factors for increased mortality in the USA from acute diarrhea include prematurity, young maternal age, rural residence, and black race [103–105].

Patients with severe hypernatremic dehydration (Na >145 mEq/L) can do well with ORT; however, they usually require correction of the free water (FW) deficit using the formula: FW deficit (in liters) = 0.6 × weight (kg) × [(patient sodium/140)−1]. (Estimated body water is 0.6 × weight in kg and 140 mEq/L is the desired sodium level.)

This is followed by maintenance of hydration with either ORT or IV fluids [106].

Dietary Therapy

Dietary therapy during maintenance hydration will vary based on the age and diet history of the patient. If an infant or child is breast or formula fed, this should continue. It is usually not necessary to use a lactose free or reduced formula, though some studies have shown some infants with malnutrition or severe dehydration recover more quickly when they are give a lactose-free formula for treatment of acute gastroenteritis [107]. Quarter or half-strength formulas have also been found to prolong resolution of symptoms and delay recovery. Soy formulas have shown a decrease in the duration of diarrhea associated with administration of antibiotics in older infants and toddlers [108]. The traditional BRAT diet (bananas, rice, applesauce, and toast) can be too restrictive and does not allow for adequate consumption of calories, which can result in severe malnourishment. It should not be recommended to with hold nutrition for 24 h, as many studies show early feeding decreases changes in intestinal permeability induced by infection and results in shorter duration of diarrhea with improved nutritional outcome [2, 103, 109]. Appropriate foods to recommend include yogurt, fruits, vegetables, complex carbohydrates (oatmeal, cornmeal, wheat), and meats, with an emphasis on maintaining caloric intake during acute episodes of emesis or diarrhea.

Pharmacologic Therapy

Adsorbents, toxin binders, antimotility, and antisecretory agents have limited data about their efficacy in older children and adults, mainly because none of these medications treats the underlying cause of the diarrhea, which is increased secretion from the intestinal crypt cells. Antiemetics, such as phenothiazines, may slow oral rehydration by causing the patient to be drowsy. The administration of the serotonin antagonist ondansetron, by either oral or IV route, has gained popularity as a medication to prevent patients from having emesis and diarrhea to prevent further dehydration.

The routine use of antimicrobial agents in the treatment of acute diarrhea may predispose the patient to antimicrobial resistance, and is not recommended. Most cases of diarrhea in developed countries are viral in nature, with the most common being rotavirus, Norovirus (in the Calicivirus

family), adenovirus, which infects children less than 2 years of age, and astrovirus, which infects infants and young children more than adults. When a bacterial source is suspected, or has been identified, antimicrobial therapy is still not often recommended, as the diarrhea is usually self-limiting and the course has not been found to be shortened by treatment with these agents. There are, however, special cases such as immunodeficiency or prematurity, when antimicrobials are necessary for treatment of acute diarrhea, but therapy should be based on the needs of the individual patient.

Other Supplemental Therapies

Studies from all over the world have demonstrated that severe zinc deficiency is associated with diarrhea, and zinc supplementation could potentially be of benefit either for improved outcomes or as prophylaxis in acute or chronic diarrhea. Patients who had low levels of zinc found on rectal biopsies had shorter duration of acute diarrhea after receiving zinc supplementation [110–112]. Clinical outcomes among patients who received zinc-fortified ORS were improved compared with those who received standard ORS, with lower total number of bowel movements in the zinc-ORS group; however, there was no significant difference between the groups in the duration of diarrhea or risk for prolonged symptoms [113]. More research is warranted to investigate how zinc can aid with treatment of AGE and to determine the best way to administer it to different patient populations.

Probiotics have been defined as "functional food" therapy, and are thought to have an effect on the physiologic process of intestinal healing in addition to the nutritional value. They function as live microorganisms in fermented foods that improve balance in intestinal flora and have been associated with reducing the duration or severity of diarrheal illnesses among pediatric patients who have been infected with rotavirus or have diarrhea from antibiotic therapy [114–116]. They are thought to compete with pathogenic bacteria for receptor sites or intraluminal nutrients. In addition, it is thought they aid in the production of antibiotic substances, and enhance host immune defenses. *Lactobacillus* and *Bifidobacteria* species have received positive reviews in studies regarding their safety and effectiveness in treating infectious diarrhea in children [117]. Despite this, it is currently difficult to obtain a consensus regarding the amount and duration of use of probiotics, as study samples are small and can have much variability in the duration of therapy.

Prebiotics, such as the oligosaccharides in human milk, are complex carbohydrates that stimulate the growth of health-promoting intestinal flora, such as *Lactobacillus* and *Bifidobacteria*. There have, however, been conflicting studies regarding their effectiveness in reducing the incidence of diarrhea in infants and children in urban areas; therefore, further studies are recommended [118].

In conclusion, the combination of oral rehydration therapy followed by early administration of nutritional support has been proven to effectively treat patients with AGE. It is essential to obtain a thorough history and physical exam in order to establish the proper degree of dehydration of the patient, and then direct the appropriate therapy.

References

1. World Health Organization. The world health report. Geneva: WHO; 1999.
2. King CK, Glass R, Bresee JS, Duggan C; Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. MMWR Recomm Rep. 2003;52(RR-16)1–16.
3. Cohen MB. Etiology and mechanisms of acute infectious diarrhea in infants in the United States. J Pediatr. 1991;118:S34.
4. Pang XL, Honma S, Nakata S, Vesikari T. Human caliciviruses in acute gastroenteritis of young children in the community. J Infect Dis. 2000;181 Suppl 2:S288.

5. Castro GA. Fluid and electrolyte absorption. In: Johnson LR, editor. Gastrointestinal physiology. St. Louis: Mosby; 2001. p. 131.
6. Field M. Intestinal ion transport and the pathophysiology of diarrhea. J Clin Invest. 2003;111:931.
7. Vanderhoof JA. Chronic diarrhea. Pediatr Rev. 1998;19:418.
8. Beers MH, Berkow R. The Merck manual of diagnosis and therapy. 18th ed. Whitehouse Station: Merck; 2006 [online] Dysentery http://www.merck.com/mmpe/sec14/ch185/ch185b.html?qt=dysentery&alt=sh.
9. Binder HJ. Causes of chronic diarrhea. N Engl J Med. 2006;355:236.
10. Bhutta ZA, Ghishan F, Lindley K, et al. Persistent and chronic diarrhea and malabsorption: Working Group report of the second World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2004;39 Suppl 2:S711.
11. Gibbons T, Fuchs GJ. Chronic enteropathy: clinical aspects. Nestle Nutr Workshop Ser Pediatr Program. 2007;59:89.
12. Ochoa TJ, Salazar-Lindo E, Cleary TG. Management of children with infection-associated persistent diarrhea. Semin Pediatr Infect Dis. 2004;15:229.
13. Finkelstein JA, Schwartz JS, Torrey S, Fleisher GR. Common clinical features as predictors of bacterial diarrhea in infants. Am J Emerg Med. 1989;7:469.
14. Bonadio WA, Hennes HH, Machi J, Madagame E. Efficacy of measuring BUN in assessing children with dehydration due to gastroenteritis. Ann Emerg Med. 1989;18:755–7.
15. Mackenzie A, Barnes G, Shann F. Clinical signs of dehydration in children. Lancet. 1989;2:605–7.
16. Yilmaz K, Karabocuoglu M, Citak A, Uzel N. Evaluation of laboratory tests in dehydrated children with acute gastroenteritis. J Paediatr Child Health. 2002;38:226–8.
17. Shaoul R, Okev N, Tamir A, Lanir A, Jaffe M. Value of laboratory studies in assessment of dehydration in children. Ann Clin Biochem. 2004;41:192–6.
18. Gupta DN, Sircar BK, Sengupta PG, et al. Epidemiological and clinical profiles of acute invasive diarrhoea with special reference to mucoid episodes: a rural community-based longitudinal study. Trans R Soc Trop Med Hyg. 1996;90:544.
19. Dutta P, Mitra U, Saha DR, et al. Mucoid presentation of acute enterocolitis in children: a hospital-based case–control study. Acta Paediatr. 1999;88:822.
20. Rothrock SG, Skeoch G, Rush JJ, Johnson NE. Clinical features of misdiagnosed appendicitis in children. Ann Emerg Med. 1991;20:45.
21. Boyce TG, Swerdlow DL, Griffin PM. Escherichia coli O157:H7 and the hemolytic-uremic syndrome. N Engl J Med. 1995;333:364.
22. Torrey S, Fleisher G, Jaffe D. Incidence of Salmonella bacteremia in infants with Salmonella gastroenteritis. J Pediatr. 1986;108:718.
23. Ashkenazi S. Shigella infections in children: new insights. Semin Pediatr Infect Dis. 2004;15:246.
24. Issenman RM, Hewson S, Pirhonen D, et al. Are chronic digestive complaints the result of abnormal dietary patterns? Diet and digestive complaints in children at 22 and 40 months of age. Am J Dis Child. 1987;141:679.
25. Talley NJ, Zinsmeister AR, Van Dyke C, Melton III LJ. Epidemiology of colonic symptoms and the irritable bowel syndrome. Gastroenterology. 1991;101:927.
26. Glass RI, Bresee J, Jiang B, et al. Gastroenteritis viruses: an overview. Novartis Found Symp. 2001;238:5.
27. Guarino A, Albano F, Ashkenazi S, et al. European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe. J Pediatr Gastroenterol Nutr. 2008;46 Suppl 2:S81.
28. Matson DO, Estes MK. Impact of rotavirus infection at a large pediatric hospital. J Infect Dis. 1990;162:598.
29. Velázquez FR, Matson DO, Calva JJ, et al. Rotavirus infections in infants as protection against subsequent infections. N Engl J Med. 1996;335:1022.
30. Doan LT, Okitsu S, Nishio O, et al. Epidemiological features of rotavirus infection among hospitalized children with gastroenteristis in Ho Chi Minh City, Vietnam. J Med Virol. 2003;69:588.
31. Subekti D, Lesmana M, Tjaniadi P, et al. Incidence of Norwalk-like viruses, rotavirus and adenovirus infection in patients with acute gastroenteritis in Jakarta, Indonesia. FEMS Immunol Med Microbiol. 2002;33:27.
32. Oh DY, Gaedicke G, Schreier E. Viral agents of acute gastroenteritis in German children: prevalence and molecular diversity. J Med Virol. 2003;71:82.
33. Jamieson FB, Wang EE, Bain C, et al. Human torovirus: a new nosocomial gastrointestinal pathogen. J Infect Dis. 1998;178:1263.
34. Yamashita T, Sakae K, Tsuzuki H, et al. Complete nucleotide sequence and genetic organization of Aichi virus, a distinct member of the Picornaviridae associated with acute gastroenteritis in humans. J Virol. 1998;72:8408.
35. Joki-Korpela P, Hyypiä T. Diagnosis and epidemiology of echovirus 22 infections. Clin Infect Dis. 1998;27:129.
36. Tucker AW, Haddix AC, Bresee JS, et al. Cost-effectiveness analysis of a rotavirus immunization program for the United States. JAMA. 1998;279:1371.

37. Ho MS, Glass RI, Pinsky PF, et al. Diarrheal deaths in American children. Are they preventable? JAMA. 1988;260:3281.
38. Rodriguez WJ, Kim HW, Arrobio JO, et al. Clinical features of acute gastroenteritis associated with human reovirus-like agent in infants and young children. J Pediatr. 1977;91:188.
39. Staat MA, Azimi PH, Berke T, et al. Clinical presentations of rotavirus infection among hospitalized children. Pediatr Infect Dis J. 2002;21:221.
40. Konno T, Suzuki H, Imai A, Ishida N. Reovirus-like agent in acute epidemic gastroenteritis in Japanese infants: fecal shedding and serologic response. J Infect Dis. 1977;135:259.
41. Arias CF, Isa P, Guererro CA, Mendez E, Zárate S, López T, Espinosa R, Romero P, López S. Molecular biology of rotavirus cell entry. Arch Med Res. 2002;33(4):356–61.
42. Chin J, editor. Control of communicable diseases manual. 17th ed. Washington: American Public Health Association; 2000.
43. Centers for Disease Control and Prevention (CDC). Preliminary food net data on the incidence of infection with pathogens transmitted commonly through food—10 states, 2009. MMWR Morb Mortal Wkly Rep. 2010;59:418.
44. American Medical Association, Centers for Disease Control and Prevention, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Food Safety and Inspection Service, US Department of Agriculture. Diagnosis and management of foodborne illnesses: a primer for physicians. MMWR Recomm Rep. 2001;50:1.
45. Glass RI, Noel J, Ando T, et al. The epidemiology of enteric caliciviruses from humans: a reassessment using new diagnostics. J Infect Dis. 2000;181 Suppl 2:S254.
46. Acheson D. Campylobacter jejuni infections: update on emerging issues and trends. Clin Infect Dis. 2001;32(8):1201–6.
47. Nachamkin I, Mishu-Allos B, Ho TW. *Campylobacter jejuni* infection and the association with Guillain–Barré syndrome. In: NachamkinI BMJ, editor. Campylobacter. 2nd ed. Washington DC: American Society for Microbiology; 2000. p. 155–78.
48. Zilbauer M, Dorrell N, Wren BW, Bajaj-Elliott M. Campylobacter jejuni-mediated disease pathogenesis: an update. Trans R Soc Trop Med Hyg. 2008;102(2):123–9.
49. Coburn B, Grassl GA, Finlay BB. Salmonella, the host and disease: a brief review. Immunol Cell Biol. 2007;85(2):112–8.
50. Grassl GA, Finlay BB. Pathogenesis of enteric Salmonella infections. Curr Opin Gastroenterol. 2008;24(1):22–6.
51. Chambers HF, McPhee SJ, Papadakis MA, Tierney LM, editors. Current medical diagnosis and treatment. 47th ed. New York: McGraw-Hill; 2008. p. 1250–2.
52. Weinberger M, Keller N. Recent trends in the epidemiology of non-typhoid Salmonella and antimicrobial resistance: the Israeli experience and worldwide review. Curr Opin Infect Dis. 2005;18(6):513–21.
53. Boyle EC, Bishop JL, Grassl GA, Finlay BB. Salmonella: from pathogenesis to therapeutics. J Bacteriol. 2007;189(5):1489–95.
54. Linam WM, Gerber MA. Changing epidemiology and prevention of Salmonella infections. Pediatr Infect Dis J. 2007;26(8):747–8.
55. Peques DA, Miller SI. Salmonella species, including Salmonella typhi (Chap. 23). In: Mandell GL, Bennett JE, Dolan R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious disease. 7th ed. Orlando: Elsevier; 2009.
56. Abubakar I, Irvine L, Aldus CF, et al. A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food. Health Technol Assess. 2007;11(36):1–216.
57. Kappeli U, Hachler H, Giezendanner N, Beutin L, Stephan R. Human infections with Non-O157 Shiga toxin-producing Escherichia coli, Switzerland, 2000–2009. Emerg Infect Dis. 2011;17(2):180–5.
58. Donnenberg MS, Kaper JB. Enteropathogenic Escherichia coli. Infect Immun. 1992;60(10):3953–61.
59. DuPont HL. Travellers' diarrhoea: contemporary approaches to therapy and prevention. Drugs. 2006;66(3):303–14.
60. Eisenstein BI, Jones GW. The spectrum of infections and pathogenic mechanisms of Escherichia coli. Adv Intern Med. 1988;33:231–52.
61. Khan WA, Dhar U, Salam MA, et al. Central nervous system manifestations of childhood shigellosis: prevalence, risk factors, and outcome. Pediatrics. 1999;103(2):E18.
62. Disease Control and Prevention, US Department of Health and Human Services; Nov 2008.
63. Edwards BH. Salmonella and Shigella species. Clin Lab Med. 1999;19(3):469–87.
64. Gomez HF, Cleary TG. Shigella species. In: Long SS, Pickering LK, Prober CG, editors. Principles and practice of pediatric infectious diseases. New York: Churchill Livingstone; 1997. p. 429–34.
65. Niyogi SK. Shigellosis. J Microbiol. 2005;43(2):133–43.

66. Ochoa TJ, Cleary TG. Shigella. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, editors. Nelson textbook of paediatrics. 18th ed. Philadelphia, PA: Saunders Elsevier; 2007. p. 1191–3.
67. Sonjai K, Soisangwan R, Sakolvaree Y, Kurazono H, Chongsa-nguan M, Tapchaisri P, Mahakunkijcharoen Y, Nair GB, Hayashi H, Chaicumpa W. Validation of salmonellosis and shigellosis diagnostic test kits at a provincial hospital in Thailand. Asian Pac J Allergy Immunol. 2001;19(2):115–27.
68. American Academy of Pediatrics. Cholera (Vibrio cholerae). In: Pickering LK, editor. Red Book: 2009 Report of the committee on infectious diseases. 28th ed. American Academy of Pediatrics: Elk Grove Village, IL; 2009. p. 727–9.
69. Centers for Disease Control and Prevention (CDC). Vibrio illnesses after Hurricane Katrina–multiple states. MMWR Morb Mortal Wkly Rep. 2005;54(37):928–31.
70. Olsen SJ, MacKinnon LC, Goulding JS, Bean NH, Slutsker L. Surveillance for foodborne-disease outbreaks–United States, 1993–1997. MMWR CDC Surveill Summ. 2000;49(1):1–62.
71. Brennt CE, Wright AC, Dutta SK. Growth of Vibrio vulnificus in serum from alcoholics: association with high transferrin iron saturation. J Infect Dis. 1991;164(5):1030–2.
72. Hor LI, Chang TT, Wang ST. Survival of Vibrio vulnificus in whole blood from patients with chronic liver diseases: association with phagocytosis by neutrophils and serum ferritin levels. J Infect Dis. 1999;179(1):275–8.
73. Miyoshi S, Nakazawa H, Kawata K, Tomochika K, Tobe K, Shinoda S. Characterization of the hemorrhagic reaction caused by Vibrio vulnificus metalloprotease, a member of the thermolysin family. Infect Immun. 1998;66(10):4851–5.
74. Mead PS, Slutsker L, Dietz V, McCaig LF, Bresee JS, Shapiro C, et al. Food-related illness and death in the United States. Emerg Infect Dis. 1999;5(5):607–25.
75. Morris JG, Black RE. Cholera and other vibrioses in the United States. N Engl J Med. 1985;312(6):343–50.
76. Daniels NA, MacKinnon L, Bishop R. Vibrio parahaemolyticus infections in the United States, 1973–1998. J Infect Dis. 2000;181(5):1661–6.
77. Shapiro RL, Altekruse S, Hutwagner L. The role of Gulf Coast oysters harvested in warmer months in Vibrio vulnificus infections in the United States, 1988–1996. Vibrio Working Group. J Infect Dis Sep. 1998;178(3):752–9.
78. Anand RG, Lopez FA, deBoisblanc B. Vibrio vulnificus sepsis successfully treated with antibiotics, surgical debridement, and recombinant human activated protein C. J La State Med Soc. 2004;156(3):130–3; quiz 133.
79. Helms M, Simonsen J, Mølbak K. Foodborne bacterial infection and hospitalization: a registry-based study. Clin Infect Dis. 2006;42(4):498–506.
80. Zheng H, Sun Y, Lin S, Mao Z, Jiang B. Yersinia enterocolitica infection in diarrheal patients. Eur J Clin Microbiol Infect Dis. 2008;27(8):741–52.
81. Young VB, Falkow S, Schoolnik GK. The invasin protein of Yersinia enterocolitica: internalization of invasin-bearing bacteria by eukaryotic cells is associated with reorganization of the cytoskeleton. J Cell Biol. 1992;116(1):197–207.
82. Handley SA, Newberry RD, Miller VL. Yersinia enterocolitica invasin-dependent and invasin-independent mechanisms of systemic dissemination. Infect Immun. 2005;73(12):8453–5.
83. Bradford WD, Noce PS, Gutman LT. Pathologic features of enteric infection with Yersinia enterocolitica. Arch Pathol. 1974;98(1):17–22.
84. Cover TL, Aber RC. Yersinia enterocolitica. N Engl J Med. 1989;321(1):16–24.
85. Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis. 2001;32(3):331–51.
86. Nylund CM, Goudie A, Garza JM, Fairbrother G, Cohen MB. Clostridium difficile infection in hospitalized children in the United States. Arch Pediatr Adolesc Med. 2011;165(5):451–7.
87. Cleary RK. Clostridium difficile-associated diarrhea and colitis: clinical manifestations, diagnosis, and treatment. Dis Colon Rectum. 1998;41(11):1435–49.
88. Starr J. Clostridium difficile associated diarrhoea: diagnosis and treatment. BMJ. 2005;331(7515):498–501.
89. Poxton IR, McCoubrey J, Blair G. The pathogenicity of *Clostridium difficile*. Clin Microbiol Infect. 2001;7:421–7. doi:10.1046/j.1198-743x.2001.00287.x.
90. Yoder JS, Harral C, Beach MJ. Giardiasis surveillance-United States, 2006–2008. MMWR Surveill Summ. 2010;59(6):15–25.
91. Thompson RC. Giardiasis as a re-emerging infectious disease and its zoonotic potential. Int J Parasitol. 2000;30(12–13):1259–67.
92. Welch TP. Risk of giardiasis from consumption of wilderness water in North America: a systematic review of epidemiologic data. Int J Infect Dis. 2000;4(2):100–3.
93. Scallan E, Hoekstra RM, Angulo FJ, Tauxe RV, Widdowson MA, Roy SL, Jones JL, Griffin PM. Foodborne illness acquired in the United States–major pathogens. Emerg Infect Dis. 2011;17(1):7–15.
94. Ravdin JI. Amebiasis. Clin Infect Dis. 1995;20:1453–66.

95. Sturchler D. Parasitic diseases of the small intestinal tract. Baillieres Clin Gastroenterol. 1987;1:397–424.
96. Stauffer W, Ravdin JI. Entamoeba histolytica: an update. Curr Opin Infect Dis. 2003;16:479–85.
97. Segarra-Newnham M. Manifestations, diagnosis, and treatment of Strongyloides stercoralis infection. Ann Pharmacother. 2007;41(12):1992–2001.
98. Ardiç N. An overview of Strongyloides stercoralis and its infections. Mikrobiyol Bul. 2009;43(1):169–77 (Review. Turkish).
99. Siddiqui AA, Berk SL. Diagnosis of Strongyloides stercoralis infection. Clin Infect Dis. 2001;33(7):1040–7.
100. Tanowitz HB, Weiss LM, Wittner M. Diagnosis and treatment of common intestinal helminths. II: Common intestinal nematodes. Gastroenterologist. 1994;2(1):39–49.
101. Albano F, Lo Vecchio A, Guarino A. The applicability and efficacy of guidelines for the management of acute gastroenteritis in outpatient children: a field-reandomized trial on primary care pediatricians. J Pediatr. 2010;156(2):226–30.
102. Duggan C, Refat M, Hashem M, Wolff M, Fayad I, Santosham M. How valid are clinical signs of dehydration in infants? J Pediatr Gastroenterol Nutr. 1996;22:56–61.
103. Duggan C, Nurko S. Feeding the gut: the scientific basis for continued enteral nutrition during acute diarrhea. J Pediatr. 1997;131:801–8.
104. Sandhu BK, European Society of Paediatric Gastroenterology, Hepatology and Nutrition Working Group on Acute Diarrhoea. Rationale for early feeding in childhood gastroenteritis. J Pediatr Gastroenterol Nutr. 2001;33(Suppl2):S13–6.
105. Nager AL, Wang VJ. Comparison of nasogastric and intravenous methods of rehydration in pediatric patients with acute dehydration. Pediatrics. 2002;109:566–72.
106. Ho MS, Glass RI, Pinsky PF. Diarrheal deaths in American children. Are they preventable? JAMA. 1988;260:3281–5.
107. Adrogue HJ, Madias NE. Hypernatremia. N Engl J Med. 2000;342(20):1493–9.
108. Brown KH, Peerson J, Fontaine O. Use of nonhuman milks in the dietary management of young children with acute diarrhea: a meta-analysis of clinical trials. Pediatrics. 1994;93:17–27.
109. Burks AW, Vanderhoof JA, Mehra S, Ostrom KM, Baggs G. Randomized clinical trial of soy formula with and without added fiber in antibiotic-induced diarrhea. J Pediatr. 2001;139:578–82.
110. Isolauri E, Juntunen M, Wiren S, Vuorined P, Koivula T. Intestinal permeability changes in acute gastroenteritis: effects of clinical factors and nutritional management. J Pediatr Gastroenterol Nutr. 1989;8:466–73.
111. Sachdev HP, Mittal NK, Mittal SK, Yadav H. A controlled trial on utility of oral zinc supplementation in acute dehydrating diarrhea in infants. J Pediatr Gastroenterol Nutr. 1988;7:877–81.
112. Strand TA, Chandyo RK, Bahl R, et al. Effectiveness and efficacy of zinc for the treatment of acute diarrhea in young children. Pediatrics. 2002;109:898–9003.
113. Penny ME, Peerson JM, Marin RM, et al. Randomized, community-based trial of the effect of zinc supplementation, with and without other micronutrients, on the duration of persistent childhood diarrhea in Lima, Peru. J Pediatr. 1999;135(2 Pt 1):208–17.
114. Bahl R, Bhandari N, Saksena M, et al. Efficacy of zinc-fortified oral rehydration solution in 6- to- 35month-old children with acute diarrhea. J Pediatr. 2002;141:677–82.
115. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr. 1995;125:1401–12.
116. Vanderhoof JA, Young RJ. Use of probiotics in childhood gastrointestinal disorders. J Pediatr Gastroenterol Nutr. 1998;27:323–32.
117. Guandalini S, Pensabene L, Zikri MA, et al. Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea: a multicenter European trial. J Pediatr Gastroenterol Nutr. 2000;30:54–60.
118. D'Souza AL, Rajkumar C, Cooke J, Bupitt CJ. Probiotics in prevention of antibiotic associated diarrhea: meta-analysis. BMJ. 2002;324:1361–6.
119. Duggan C, Penny ME, Hibberd P, et al. Oligofructose-supplemented infant cereal: 2 randomized, blinded, community-based trials in Peruvian infants. Am J Clin Nutr. 2003;77:937–42.
120. Gilger MA. Pathogenesis of acute diarrhea in children. In: Basow DS, editor. UpToDate. UpToDate: Waltham; 2011.
121. Fleisher GR. Evaluation of diarrhea in children. In: Basow DS, editor. UpToDate. Waltham: UpToDate; 2011.
122. Matson DO. Epidemiology, pathogenesis, clinical presentation and diagnosis of viral gastroenteritis in children. In: Basow DS, editor. UpToDate. Waltham: UpToDate; 2011.
123. Duggan C, Santosham M, Glass RI. The management of acute diarrhea in children: oral rehydration, maintenance, and nutritional therapy. MMWR Recomm Rep. 1992;41(No. RR-16):1–20.
124. World Health Organization. The treatment of diarrhoea; a manual for physicians and other senior health workers. Geneva: World Health Organization; 1995. Available at http://www.who.int/child-adolescent-health/New_Publications/CHILD_HEALTH/WHO.CDR.95.3.htm
125. Tarr PI, Gordon CA, Chandler WL. Shiga-toxin-producing Escherichia coli and haemolytic uraemic syndrome. Lancet. 2005;365(9464):1073–86.

Chapter 11
Celiac Disease in Infants: Prevention and Dietary Treatment

Mukadder Ayşe Selimoğlu

Key Points

- The most important preventive factor for celiac disease development is the breastfeeding.
- Introduction of small amounts of gluten during the fourth to sixth month of age, while the infant is still breastfed should be encouraged.
- Although novel therapies are under investigation, a lifelong gluten-free diet is the only effective and reliable treatment at present.

Keywords Micronutrient supplementation • Celiac disease • Breast milk • Gluten-free diet

Celiac disease (CD) is the most common malabsorption in the world, and is a major healthcare issue. It is an immune-mediated gluten-dependent enteropathy, which has a wide range of clinical manifestations and variable severity. It is triggered by the ingestion of gluten, which is found in wheat, rye, and barley, in genetically susceptible individuals. While typical clinical manifestations of CD include failure to thrive, chronic diarrhea, and anemia, a significant proportion of patients present with atypical symptoms, such as skin lesions, isolated hypertransaminasemia, dental or neurological problems [1–3]. A changing pattern in the presentation of pediatric CD, such as a more frequent diagnosis in older children, mostly presents with atypical symptoms, is reported [4]. Typical (classical) CD is more common in younger children (mainly between 6 and 18 months of age) and frequently is associated with more severe intestinal injury [5].

As the treatment of such a prevalent disorder costs much and is restrictive, prevention is a better strategy. Although no treatment modality other than a gluten-free diet (GFD) is practically available in CD, it is promising to see increasing numbers of studies focused on the novel treatment efforts.

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Prevention

Cessation of breastfeeding (BF) before the introduction of gluten, consumption of high amounts of gluten, and early introduction of gluten-containing foods into the diet of the infants are proposed hypotheses in the development of CD. "The Swedish epidemics of CD," where annual incidence rate in children below 2 years of age increased fourfold in 1980s lasting for a nearly decade with an abrupt decline beginning in 1995, is an important phenomenon suggesting the importance of BF in the prevention of CD [6]. The differences between high and low incidence periods were reported as doubled BF rates and decreased flour consumption [6]. Postponement of gluten introduction from fourth to sixth month, and introduction of gluten in smaller amounts from fourth months of age, while the child is still being breastfed, suggested by two national recommendations, worth mentioning in respect with the decreased incidence of CD in the following years [6].

BF duration is another subject of interest; studies showed that BF duration less than 90 days and 30 days increased the risk of developing CD 5 and 4 times, respectively [7, 8]. BF more than 2 months decreased the risk by 63 % [9]. Mean BF duration of children with CD was reported to be shorter than that of healthy children [10]. However, The Diabetes Autoimmunity Study in the Young (DAISY) project did not provide evidence on the protective role of prolonged breastfeeding, may be due to the fact that the study was conducted on high risk children [11, 12].

It seems that BF has an independent protective effect against CD if the infants are breastfed at the time when gluten-containing foods were introduced [10]. In a meta-analysis, it was shown that children being breastfed at the time of gluten introduction had 52 % reduction in CD risk [13]. From another perspective, a higher chance of developing CD was seen in babies who were not given gluten when weaned off breast milk [14].

It was estimated that if all babies were breastfed in the UK at the time of gluten introduction, more than 2,500 cases of CD per year would be prevented [14].

It was also suggested that BF affects the presentation of CD; in exclusively breastfed children, symptomatic CD developed later and they had lower rates of failure to thrive and short stature [15]. Interestingly, in another study, children breastfed at the time of gluten introduction were just as likely to develop intestinal as extra-intestinal symptoms, whereas children who were not breastfed when weaned with gluten had a much higher chance of showing intestinal symptoms [12].

How BF protects infants from CD development is unclear although prevention via decreased gastrointestinal infections and limited consumption of gluten due to BF are suggested mechanisms [13]. Breast milk IgA antibodies may diminish immune response to gluten in addition to the T-cell specific suppressive effect of human milk [16].

Scandinavian paradox is another prompting phenomenon for the investigation of CD pathogenesis. In comparison to CD rates in Sweden, the rates in Estonia were found lower, possibly reflecting the later and decreased dietary exposure of Estonian infants to gluten as compared with Swedish infants [17, 18]. In an epidemiologic study, it was shown that children with CD consumed larger amounts of flour compared with others [10]. The difference in the incidence of CD between Northern and Southern India, where wheat and rice, respectively, are the staple foods further suggested that the amount of gluten is an important factor in the development of CD [19].

Both early (<3 months after birth) and late (>7 months after birth) introduction of gluten increased the risk of CD autoimmunity, which was defined as positive tissue transglutaminase antibody (tTG Ab) on two or more consecutive visits or a positive tTG Ab and a small bowel biopsy consistent with CD [11]. That conclusion was drawn from a 10-year observational study that investigated the age at first introduction of gluten-containing cereals in large series at risk of CD or type 1 diabetes in relation to the subsequent risk of developing CD autoimmunity [11]. In the mentioned study, children exposed to gluten in the first 3 months of age had a fivefold increased risk of CD autoimmunity compared to those exposed at 4–6 months [11]. Furthermore, those who received gluten for the first time at 7 months of age or after showed a slightly increased hazard ratio compared with those exposed at 4–6 months [11].

A suggested preventive measure other than BF and appropriate timing of gluten is the gastrointestinal infections, which might increase gut permeability leading to increased antigen penetration and may drive the immune system toward a T-helper 1-type response typical for CD [20]. Rotavirus was suggested as a triggering agent because frequent rotavirus infections predicted a higher risk of CD autoimmunity, and hence rotavirus vaccination was suggested as a preventive measure [21, 22].

Difference between microbiota and, as a result, short chain fatty acid composition in intestinal tract of children with or without CD suggested a potential role of gut microbiota in CD [23, 24]. This is relevant to BF practices however needs comprehensive studies.

As a conclusion, the duration of BF, BF when gluten is introduced into the diet, age at gluten introduction, and amount of gluten in diet are considered as potential factors influencing incidence and age at onset of CD. The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee recommended avoidance of both early (<4 months) and late (>7 months) introduction of gluten and introduction of small amounts of gluten gradually while the child is still breastfed [25]. It is believed that BF during that window phase contributes to the modulation of mucosal immune response and maturation of the gastrointestinal system [12].

Treatment

History

Samuel Gee, modern-day describer of the disease in 1888, could not find the cause of CD but thought it should be diet, which would cure the disease. He considered milk, highly starched foods, rice, sago, fruits, and vegetables as unsafe, and recommended raw meat, bread, and mussels, at that time. In 1908, Christian Archibald Herter noted that fat was better tolerated than carbohydrate in his book on children with CD. Sydney Haas reported positive effects of a diet of bananas in 1924, and excluded bread, crackers, cereals, and potatoes in that diet, probably unintentionally. This dietary treatment was applied to children with CD during Second World War years. Willem Dicke who observed clinical improvement of his patients during the time period, in which flour was sparse due to war, and relapse of the disease after Swedish planes dropped bread into the Netherlands accused wheat of being the cause of CD in the 1940s [26]. In 1950, Dicke established that exclusion of wheat, rye, and oats from the diet led to dramatic improvement. The toxicity was then shown to be due to a protein component, referred to as gluten [27].

Gluten-Free Diet

A lifelong strict GFD has been the cornerstone treatment for CD since then [28]. A lifelong GFD is a well-tolerated therapy that improves health and quality of life in the vast majority of patients with CD, even in those with minimal symptoms. However, it has a large number of restrictions on the patients through social and financial implications. In addition to restrictive nature, palatability, insufficient education, and misinformation, variations in food labeling and possible cross contamination are the causes of non-adherence to diet [29].

It is very important at the beginning of the diagnosis to ensure parents of infants with CD, to which foods are allowed and which are not. It is very important to give details of the diet beginning with common foods however; foods that may be consumed occasionally should be mentioned in respect with their gluten content, as well. Although infants consume a more limited diet, concern of the parents that “a limited diet is an unhealthy diet” may lead them to try more foods than needed. Therefore,

it is critical that all parents ensure that each product is gluten-free by carefully reading food labels. Lists of gluten-containing and gluten-free foods should be provided.

Gluten-free foods must be stored and prepared separately, cooking and serving utensils must be cleaned carefully prior to use [29].

Gluten-free products are easily available in developed countries, albeit at a greater expense than gluten-containing foods [29]. In developing world, corn flour/starch, potato flour/starch, tapioca flour/starch, and rice flour are commonly used for gluten-free baking. Amaranth, arrowroot, bean flours, buckwheat, flax seed, millet, nut flour, pea's flour, quinoa, rice, sago, sorghum flour, soy flour, and teff are other allowed gluten-free foods [29]. Although meat, milk and fresh fruits and vegetables are safe, toasted, and fried dried fruits, especially if they contain salt, jellies, sweet and fruit purees, and margarines containing fiber are not gluten-free [30].

The availability of gluten-free foods increases a patient's food choices and improves diet variety while allowing patients and parents to feel "normal" when eating among their peers [29]. It should be kept in mind that gluten-free products might be high in fat and calories, a strategy to enhance the acceptability of those foods [29, 31, 32]. Furthermore, it was found that many gluten-free cereal products contain inferior amounts of thiamin, riboflavin, niacin, folate, and iron compared with the enriched wheat products that they are intended to replace [29].

Gluten contamination in gluten-free products cannot be totally avoided [29]. The accepted definition for "gluten-free" of the Codex Committee on Nutrition and Foods for Special Dietary Uses is as follows: "gluten-free foods should not contain gluten higher than 20 mg/kg in total." Some authors propose 100 mg/kg as a safe limit for gluten-free foods [33]. In a multicenter, double blind, placebo-controlled, randomized trial in adults revealed that the ingestion of gluten should be kept lower than 50 mg/day in the treatment of CD [34]. Collin et al. [35] found that 30 mg/day gluten intake did not harm CD mucosa in the long-term. The individual variability should also be kept in mind [33, 34]. There is not any specific study on infants investigating the threshold of gluten intake.

Oats

Oats are considered safe for patients with CD unless contaminated by gluten. A study showed that long-term consumption of oats is well tolerated by children with CD in remission [36]. In a systematic review, it was shown that 1 of 165 patients was diagnosed to have histological damage due to oat consumption [37]. Although there is now evidence suggesting oats lacking toxicity for patients with CD, there is a small subset of patients who do not tolerate oats, bloating and abdominal discomfort being the main complaints [38]. As the contamination of oats by gluten is not rare [39], oats consumption allowance after remission with a strict GFD, so that possible adverse reactions can be readily identified, and recommendations by national societies in respect with oats consumption may make sense. Another issue that warrants further investigations is related to the great heterogeneity of oats cultivars; more studies are needed to assess possible different in vivo toxicities of different oats cultivars for patients with CD [37]. Oats up to 20–25 g/day for children can be consumed.

Lactose Intolerance

Secondary lactose intolerance resulting from decreased lactase production by the damaged villi is common, especially in infants [29]. In many cases, lactose intolerance resolves naturally with time on the GFD, however, a lactose-free diet is indicated, especially in infants, if symptoms of lactose intolerance, such as watery diarrhea, bloating, diaper dermatitis, or persistent diarrhea despite GFD, exist.

Malnutrition

In classical CD, malnutrition is not rare. Degree of malnutrition can be determined by a comprehensive nutritional assessment. Nutritional treatment of those infants is planned in accordance with general rules for malnutrition, except allowance of gluten-containing foods. Higher nutrient needs because of intestinal loss should be kept in mind however; in severe malnutrition, avoidance of refeeding syndrome due to excessive nutrient supplementation at the beginning is critical. Enteral nutrition support with formulas including medium-chain triglycerides, oligopeptides, and/or amino acids is recommended [30].

Micronutrient Supplementation

Iron-deficiency anemia in CD is common and is reportedly higher in patients with long-standing, untreated disease [29]. Although folate and cobalamin deficiencies are known complications of CD, the most common nutritional anemia is associated with iron deficiency. Treatment with a GFD without iron medication usually eliminates iron deficiency [40]. However, in a pediatric study, it was shown that in children with CD, iron-deficiency state continues for a longer time even after excluding gluten from the diet and iron supplementation [41]. It was suggested that apart from offering them GFD rich in iron, early iron supplementation would contribute to their mental and psychomotor functions [41]. If iron supplements are required, it could be advisable to keep using them for up to 6 months after beginning the GFD, the minimum period to normalize the intestinal anatomy [30]. In any case, supplements should be administered with foods rich in vitamin C to optimize their dosage [30].

Deficiency of folate and vitamin B12 needs supplementation [29]. Fat-soluble vitamin deficiencies, especially vitamin K deficiency, may be encountered in patients with classic malabsorption; when detected they should be repleted [29].

Calcium, phosphorus, and vitamin D deficiencies may occur due to malabsorption or a lactose-free diet when applied. D vitamin deficiency may become evident after acceleration of growth; thus even though there is not any manifestation of rickets at the time of diagnosis; infants should be examined from that perspective at every visit. Adequate dietary intake of calcium and vitamin D supplementation is essential in infancy.

Patients with CD have been reported to be deficient in vitamin B6, copper, selenium, and zinc, however, screening and supplementation is not recommended because these deficiencies reverse rapidly once patients start following a GFD [30].

Adherence to Diet and Follow-Up

Reassessment of the diet at each visit with the help of an experienced dietician is a noninvasive and simple way to ensure GFD compliance. The complete resolution of symptoms in the previously symptomatic child is a strong supportive evidence that the patient is adhering to diet treatment [42]. Failure of the tissue transglutaminase antibody level to decline over a period of 6 months after starting the GFD suggests continued ingestion of gluten or related products [42, 43]. Duodenal biopsy is the gold standard to determine the response to GFD, however, at present a follow-up biopsy is not indicated for those who are clinically recovered.

Parents have a very important impact on maintaining a strict GFD in infants.

Treatment of children with CD aims to relieve symptoms, heal the intestine, and reverse the consequences of malabsorption [44]. It was reported that 70 % of patients reported an improvement in symptoms within 2 weeks of initiating the GFD [45]. While growth and development in children returns to normal with GFD, even obesity may develop [46].

Novel Non-dietary Treatments

Despite its harmlessness, the restrictive nature of a strict GFD induced new investigations aiming for easier and more comfortable treatment modalities. These alternative treatments should be as safe and efficient as GFD, and should lead an increased quality of life with a high compliance. At present, there are several options that are being investigated such as enzyme supplementation, correction of the intestinal barrier defect against gluten entry, blocking of gliadin presentation by HLA blockers and tissue transglutaminase inhibitors, cytokines, and anticytokines, modified gluten peptides, and stem cell transplantation [47].

Conclusions

The most important preventive strategies include the encouragement of BF and the introduction of small amounts of gluten during the fourth to sixth month of age. The most reliable treatment of CD remains the GFD. However, lifelong dietary restriction of gluten has many difficulties both socially and medically. Avoiding gluten completely is nearly impossible as it is widely used in many food products and contamination is common. In an effort to circumvent some of these problems, newer prevention and treatment strategies are being investigated.

References

1. Troncone R, Ivarsson A, Szajewska H, et al. Review article: future research on coeliac disease-a position report from the European multistakeholder platform on coeliac disease (CDEUSSA). Aliment Pharmacol Ther. 2008;27:1030–43.
2. Farrell RJ, Kelly CP. Celiac sprue. N Engl J Med. 2002;346:180–8.
3. Fasano A. Clinical presentation of celiac disease in the pediatric population. Gastroenterology. 2005;128:S68–73.
4. Roma E, Panayiotou J, Karantana H, et al. Changing pattern in the clinical presentation of pediatric celiac disease: a 30-year study. Digestion. 2009;80:185–91.
5. McGowan KE, Castiglione DA, Butzner JD. The changing face of childhood celiac disease in North America: impact of serological testing. Pediatrics. 2009;124:1572–8.
6. Ivarsson A, Persson LA, Nystrom L, et al. Epidemic of coeliac disease in Swedish children. Acta Paediatr. 2000;89:165–71.
7. Greco L, Mayer M, Grimaldi M, et al. The effect of early feeding on the onset of symptoms in celiac disease. J Pediatr Gastroenterol Nutr. 1985;4:52–5.
8. Auricchio S, Follo D, de Ritis G, et al. Does breastfeeding protect against the development of clinical symptoms of celiac disease in children? J Pediatr Gastroenterol Nutr. 1983;2:428–33.
9. Peters U, Schneeweiss S, Trautwein EA, et al. A case–control study of the effect of infant feeding on celiac disease. Ann Nutr Metab. 2001;45:135–42.
10. Ivarsson A, Hernell O, Stenlund H, et al. Breast-feeding protects against celiac disease. Am J Clin Nutr. 2002;75:914–21.
11. Norris JM, Barriga K, Hoffenberg EJ, et al. Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. JAMA. 2005;293:2343–51.
12. Silano M, Agostoni C, Guandalini S. Effect of the timing of gluten introduction on the development of celiac disease. World J Gastroenterol. 2010;16:1939–42.
13. Akobeng AK, Ramanan AV, Buchan I, et al. Effect of breast feeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies. Arch Dis Child. 2006;91:39–43.
14. Akobeng AK, Heler RF. Assessing the population impact of low rates of breast feeding on asthma, coeliac disease and obesity: the use of a new statistical method. Arch Dis Child. 2007;92:483–5.
15. D'Amico MA, Holmes J, Stavropoulos SN, et al. Presentation of pediatric celiac disease in the United States: prominent effect of breastfeeding. Clin Pediatr (Phila). 2005;44:249–58.

16. Juto P, Meeuwisse G, Mincheva-Nilsson L. Why has coeliac disease increased in Swedish children? Lancet. 1994;343:1372.
17. Mitt K, Uibo O. Low cereal intake in Estonian infants: the possible explanation for the low frequency of coeliac disease in Estonia. Eur J Clin Nutr. 1998;52:85–8.
18. Weile B, Krasilnikoff PA. Low incidence rates by birth of symptomatic coeliac disease in a Danish population of children. Acta Paediatr. 1992;81:394–8.
19. Gupta R, Reddy DN, Makharia GK, et al. Indian task force for celiac disease: current status. World J Gastroenterol. 2009;15:6028–33.
20. Ivarsson A, Hernell O, Nystrom L, et al. Children born in the summer have an increased risk for coeliac disease. J Epidemiol Community Health. 2003;57:36–9.
21. Stene LC, Honeyman MC, Hoffenberg EJ, et al. Rotavirus infection frequency and risk of celiac disease in early childhood: a longitudinal study. Am J Gastroenterol. 2006;101:2333–40.
22. Troncone R, Auricchio S. Rotavirus and celiac disease: clues to the pathogenesis and perspectives on prevention. J Pediatr Gastroenterol Nutr. 2007;44:527–8.
23. Schippa S, Iebba V, Barbato M, et al. A distinctive 'microbial signature' in celiac pediatric patients. BMC Microbiol. 2010;10:175.
24. Collado MC, Calabuig M, Sanz Y. Differences between the faecal microbiota of coeliac infants and healthy controls. Curr Issues Intest Microbiol. 2007;8:9–14.
25. Agostoni C, Decsi T, Fewtrell M, et al. Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2008;46:99–110.
26. Paveley WF. From Aretaeus to Crosby: a history of coeliac disease. BMJ. 1988;297:1646–9.
27. Losowsky MS. A history of coeliac disease. Dig Dis. 2008;26:112–20.
28. Guandalini S, Gupta P. Celiac disease: a diagnostic challenge with many facets. Clin Appl Immunol Rev. 2002;2:293–305.
29. Niewinski MM. Advances in celiac disease and gluten-free diet. J Am Diet Assoc. 2008;108:661–72.
30. Garcia-Manzanares A, Lucendo AJ. Nutritional and dietary aspects of celiac disease. Nutr Clin Pract. 2011;26:163–73.
31. Thompson T. Thiamin, riboflavin, and niacin contents of the gluten free diet: is there cause for concern? J Am Diet Assoc. 1999;99:858–62.
32. Thompson T. Folate, iron, and dietary fiber contents of the gluten free diet. J Am Diet Assoc. 2000;100:1389–96.
33. Collin P, Maki M, Kaukinen K. Safe gluten threshold for patients with celiac disease: some patients are more tolerant than others. Am J Clin Nutr. 2007;86:260.
34. Catassi C, Fabiani E, Iacono G, et al. A prospective, doubleblind, placebo-controlled trial to establish a safe gluten threshold for patients with celiac disease. Am J Clin Nutr. 2007;85:160–6.
35. Collin P, Maki M, Kaukinen K. It is the compliance, not milligrams of gluten, that is essential in the treatment of celiac disease. Nutr Rev. 2004;62:490.
36. Holm K, Maki M, Vuolteenaho N, et al. Oats in the treatment of childhood coeliac disease: a 2-year controlled trial and a long-term clinical follow-up study. Aliment Pharmacol Ther. 2006;23:1463–72.
37. Lundin KE, Nilsen EM, Scott HG, et al. Oats induced villous atrophy in coeliac disease. Gut. 2003;52:1649–52.
38. Troncone R, Auricchio R, Granata V. Issues related to gluten-free diet in coeliac disease. Curr Opin Clin Nutr Metab Care. 2008;11:329–33.
39. Valdes I, Garcia E, Llorente M, et al. Innovative approach to low-level gluten determination in foods using a novel sandwich enzyme-linked immunosorbent assay protocol. Eur J Gastroenterol Hepatol. 2003;15:465–74.
40. Stahlberg MR, Savilahti E, Siimes MA. Iron deficiency in coeliac disease is mild and it is detected and corrected by gluten-free diet. Acta Paediatr Scand. 1991;80:190–3.
41. Kapur G, Patwari AK, Narayan S, et al. Iron supplementation in children with celiac disease. Indian J Pediatr. 2003;70:955–8.
42. Hill ID, Dirks MH, Liptak GS, et al. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2005;40:1–19.
43. Briani C, Samaroo D, Alaedini A. celiac disease: from gluten to autoimmunity. Autoimmun Rev. 2008;7:644–50.
44. See J, Murray JA. Gluten-free diet: The medical and nutrition management of celiac disease. Nutr Clin Pract. 2006;21:1–15.
45. Green PHR, Stavropoulos SN, Panagi SG, et al. Characteristics of adult celiac disease in the USA: Results of a national survey. Am J Gastroenterol. 2001;96:126–31.
46. Reilly NR, Aguilar K, Hassid BG, et al. Celiac disease in children with normal weight and overweight: clinical features and growth outcomes following a gluten-free Diet. J Pediatr Gastroenterol Nutr. 2011;53(5):528–31.
47. Sollid LM, Khosla C. Novel therapies for coeliac disease. J Intern Med. 2011;269:604–13.

Chapter 12
The Nutritional Aspects of Intestinal Failure Therapy

Jeffrey A. Rudolph

Key Points

- Nutrition is a critical component in the multifaceted approach to infants with intestinal failure.
- Nutritional management in intestinal failure is considered both supportive and therapeutic.
- The ability to adequately assess growth is essential in the nutritional management of infants with intestinal failure due to the negative effects of both under- and over-nutrition.
- While there are multiple pathways to attempt intestinal rehabilitation, the overall goal in therapy is the attainment of oral autonomy.
- When accounting for the overall differences in short term vs. chronic administration, parenteral nutrition can generally be delivered safely while minimizing complications such as parenteral nutrition associated liver disease.

Keywords Intestinal failure • Enteral nutrition • Oral autonomy • Parenteral nutrition • Parenteral nutrition associated liver disease

Introduction

Perhaps in no other pathophysiological state in infancy are the tenets of nutritional management more thought provoking as they are in intestinal failure therapy. Intestinal failure is the critical reduction of functional gut mass below the minimal amount necessary for adequate digestion and absorption to satisfy body nutrient and fluid requirements in adults or growth in children [1]. This definition implies an absolute requirement for parenteral nutrition in order to sustain viability. The unique aspects of management in this population of patients is derived from the variability of individual physiologic states, the chronicity in which parenteral nutrition must be administered, the therapeutic implications of enteral nutrients, and the complications directly linked to nutritional therapy. The goal of this chapter is to outline the nutritional aspects of intestinal failure management highlighting the specific aspects that make it such a challenging condition.

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Intestinal Failure in the Pediatric Patient

Critical to understanding intestinal failure as a distinct entity is the concept that it is a functional, not anatomical diagnosis. Classically, the short gut syndrome, an anatomical reduction of gut mass secondary to conditions such as necrotizing enterocolitis, complicated gastroschisis, atresia, volvulus, or any combination of these and other entities continue to make up the majority of the intestinal failure population [2]. The nutritional needs of this population, especially pertaining to fluids and electrolytes, are dependent upon factors such as the length of resection [3, 4], the site where the resection occurred and the reestablishment of continuity with the colon [4], and the motility of the remaining intestine. Complicating the picture further are patients in which the predicted gut length should be sufficient to maintain enteral tolerance but cannot, as in motility disorders such as long segment aganglionosis or pseudo-obstruction syndromes. Finally, the congenital enteropathies in which an inherent defect in intestinal mucosa function cannot maintain viability without parenteral nutrition support are yet another unique subgroup within the intestinal failure population.

The overall goal of intestinal failure therapy, termed intestinal rehabilitation, is the attainment of oral autonomy. In cases where intestinal failure is irreversible, the goal shifts to a supportive one by maintaining fluid, electrolyte, and nutritional requirements indefinitely or until a more definitive corrective measure such as small bowel transplantation is employed. The care of infants with intestinal failure crosses over many disciplines and often requires contributions of multiple care teams (Fig. 12.1). Of these, nutritional management plays a major role.

Growth in Intestinal Failure

Satisfactory growth is a requisite goal in any nutritional management strategy for infants and children. Growth is routinely assessed against standard anthropometric data such as the World Health Organization (WHO) and Centers for Disease Control (CDC) growth charts. While these data sources have proven invaluable in the assessment of normal infant and childhood growth, there has been recognition of their limitations in children with specific conditions such as very low birth weight infants [5], trisomy 21 [6], and a number of other clinical diagnoses. The establishment of a consensus for

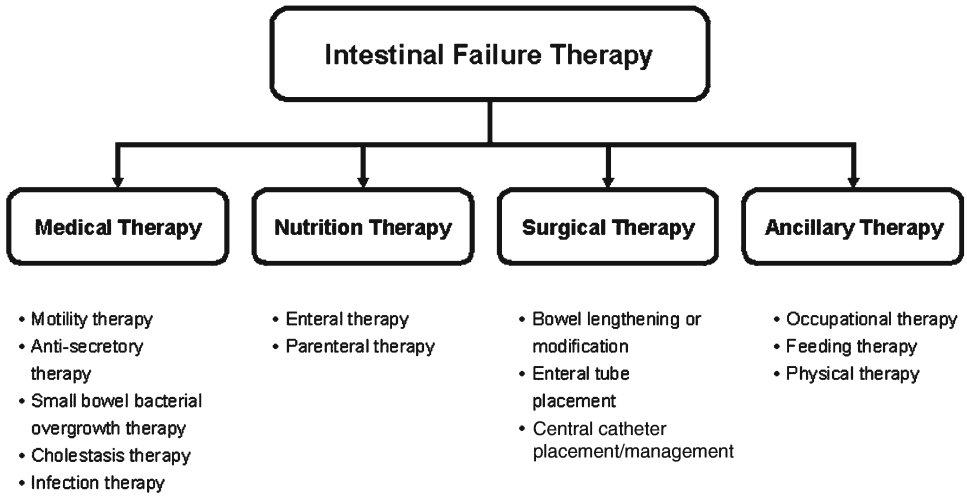

Fig. 12.1 Examples of the multidisciplinary therapies involved in intestinal failure management

ideal growth in children with intestinal failure is problematic in that it represents a unique population without standardized data in which to compare individuals against a norm.

The long term effect of short gut syndrome on growth is controversial with some reports suggesting a normal height and weight in patients that have weaned from TPN [3, 7] while others have noted a decreased weight for age and height for age in a similar population [8]. Thus, there is a lack of clarity with regards to the long term expectations of children with regard to growth in intestinal failure. Secondly, the calories provided in parenteral nutrition is an iatrogenic variable in which weight gain can be imposed to differing degrees, thereby providing the practitioner an opportunity to "fit" the child to a growth curve. The consequences of potential over-nutrition through TPN can be a potential nidus for the development of complications, such as parenteral nutrition associated liver disease. Therefore the assessment of growth through charts developed for healthy infants can be limited.

Despite the lack of information on standardized growth of children with intestinal failure, the critical component in measuring growth is that of continued and consistent weight gain over time. The use of weight for height measurements may prove to be most useful as it implies symmetrical growth over time. The estimated caloric needs in intestinal failure are generally derived by monitoring growth. Oftentimes, in infants maintained exclusively on TPN, the caloric need is less than in orally fed infants as it is not dependent upon intestinal absorption. In patients with an enteral contribution, overall caloric administration is greater than that in oral fed infants alone due to malabsorption. All nutritional therapy in intestinal failure must be achieved through the diligent monitoring of growth and the provision of adequate calories to maintain growth.

Enteral Feeding Therapy

In intestinal failure, enteral feeding is unique in that it provides both nutritional support and serves as primary therapy in the rehabilitative process. The variability in the types, amounts, and routes of feeding, along with a lack of a unified, evidenced-based approach to feeding makes this aspect of care one of the most challenging and complex aspects of intestinal rehabilitation.

Therapeutic Enteral Feeding

The physiologic process that drives rehabilitation is termed adaptation in which there is a gradual increase in the intestinal absorptive capacity to compensate for the loss of functional gut mass. Conceptually, adaptation is largely confined to the anatomical loss of intestine rather than normal length dysfunctional bowel, although rarely patients with a full complement of dysfunctional intestine may come to realize at least a minimal amount of enteral feeds. The mechanisms underlying adaptation remain elusive but are likely hormonal in nature as demonstrated by early parabiosis models in rats [9]. To date, there have been a number of trials using various single hormonal therapies such as epidermal growth factor [10], growth hormone and glutamine [11, 12], and glucagon like peptide-2 [13] that have met with varied results. The hormonal milieu that occurs during feeding is widespread and varied. The ability to recapitulate the hormonal response to oral feeds is a basis for using enteral nutrition as a primary promoter of intestinal adaptation. In a small study of infants with chronic diarrhea randomized to TPN alone or TPN in combination with continuous enteral feeds, the enteral feeding group had a quicker resolution of symptoms despite similar patterns of growth [14]. While this is not clear evidence of intestinal adaptation in anatomically short gut, it does suggest the benefits of feeds on intestinal mucosal function.

Enteral feeds can also be viewed as therapeutic with regard to the prevention and or treatment of parenteral nutrition associated liver disease (PNALD). PNALD is one of the major morbidities in

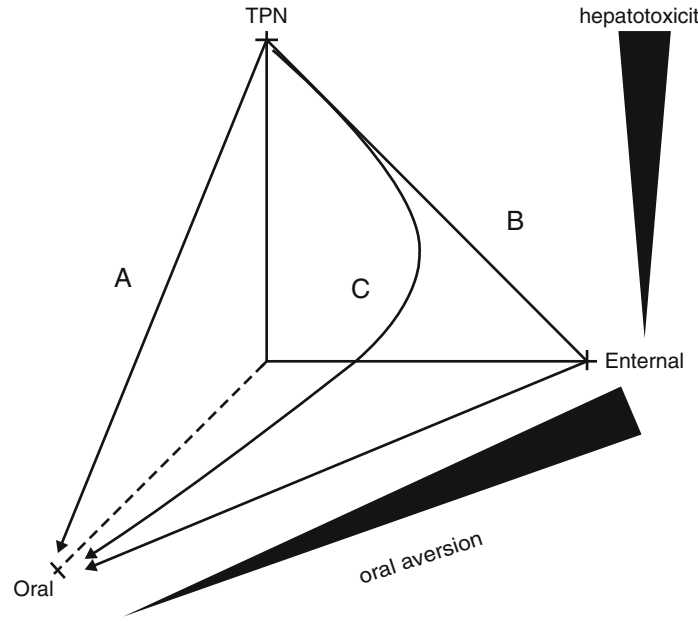

Fig. 12.2 The triad of nutritional therapy in intestinal failure: (**a**) transition from TPN to oral therapy in absence of an enteral feeding tube, (**b**) advancement to full enteral tube feeds prior to oral advancement, and (**c**) a combination of oral and enteral feeds as TPN is weaned. The risk for hepatotoxicity in TPN therapy drives therapy towards enteral/oral feeds. The degree of oral aversion limits the capacity to attain oral tolerance

intestinal failure therapy and thought to be multifactorial, though recent theories have focused on lipid administration (see below). Weaning parenteral nutrition as enteral feeds are advanced can potentially reverse cholestasis. A plateau effect on bilirubin levels is seen as enteral feeds approach 60 % with hyperbilirubinemia resolution roughly 4 months after cessation of TPN [15].

Enteral Feeding in Intestinal Failure

The ultimate goal of intestinal rehabilitation therapy is oral autonomy. To this end, there are multiple pathways to transition feeds from total parenteral nutrition to oral autonomy. Parenteral nutrition can be weaned as oral feeds increase, as enteral therapy *via* a feeding tube is administered, or often, a combination of both (Fig. 12.2). The factors determining how feeds are established are often clinician- and patient-dependent. The factors include the presence or absence of an enteral feeding tube, gastrointestinal motility, degree of oral aversion, and comorbidity (such as neurological status, risk of aspiration, etc.).

Strictly speaking from the standpoint of energy balance, continuous feeding appears to result in greater nutritional benefit. In a randomized cross-over study in adult patients with short gut syndrome, the provision of continuous feeds vs. oral feeds alone resulted in greater absorption of calories, protein, and lipid [16]. While this has not been studied in children, the implication would suggest an increased enteral:parenteral nutrition ratio to the point at which stool output becomes a limiting factor. After this point is reached, the process of adaptation will begin to dictate the rate of advancement. There is currently no data to suggest whether continuous, bolus, or oral bolus feeds are more likely to promote adaptation, although adaptive benefits may be derived from salivary epidermal growth factor [17] or other hormones when oral feeds are utilized. It is possible that when an enteral tube is available for night time feeds a combination of both strategies will provide an optimum balance of nutritional therapy and stimulation of adaptation.

In addition to the route and method of feeding, the choice of enteral product must be considered. Consensus appears to favor breast milk as an optimal choice and has been correlated with a decreased time on TPN [18] and is a major provider of epidermal growth factor in the neonatal period [19]. When breast milk is not available, the choice of infant formulas can be based upon the balance between

macronutrient absorption and adaptation. Central to the role of enteral nutrition in adaptation is the concept of the functional workload of the enterocytes with more complex nutrients providing greater work for digestion and mucosal stimulation [20]. Studies in rats show enhanced adaptation in using disaccharides over monosaccharides [21], whole protein over hydrosylate [22], and long chained triglycerides over medium chained triglycerides [23]. The provision of more complex formula must be balanced by the disadvantages including the osmotic effect produced by a relative dissacharidase deficiency in resected bowel, exposure to complex proteins and risk of sensitization, and the absorptive capacity of medium chained triglycerides over long chained triglycerides. In practice, protein hydrosylate or elemental formulas are most often used, which generally contain simple carbohydrate sources and variable fat sources. Despite the low complexity of protein content in elemental formula, it has been associated with a decreased time on TPN [18] and the ability to advance feeds and wean TPN when switched from hydrosylate formulas [24]. Whether this solely reflects the protein composition or the other components of the formula is currently unknown.

Oral Feeds

The introduction of oral feeds is important in normal infant oral motor development critical to infancy. In contrast to the hyperphagia that commonly affects older children and adults with short gut syndrome [25], infants with intestinal failure will often exhibit oral aversion [26]. While the mechanisms of oral aversion are not clearly defined, the innate neurophysiological pathways present at birth are likely lost without use [27]. While these can be regained, it is often more difficult as infancy progresses. This has led to a common practice of oral stimulation as early as possible [28] including non-nutritive oral stimulation progressing to nutritive stimulation and finally limited oral feeding as the clinical situation dictates.

Most children with intestinal failure during parenteral nutrition administration as well as afterwards will rely on formula feeding to provide enteral calories. However, solid feeds are often used as a supplemental nutritional source. Solids feeds are advantageous in that they are part of the continuum of normal infant feeding and provide psychological benefit to parents who are striving for a degree of normalcy in a child with a chronic intestinal illness. Solids, if chosen carefully can provide soluble fiber which can serve physiological benefit including water retention and caloric absorption due to colonic fermentation into short chain fatty acids and subsequent absorption. There may also be additional benefit in providing a stimulus for mucosal adaptation. Fiber, in some cases can be added to formula to derive these benefits.

Similar to normal infant feeding, rice cereal with up to 0.5 g soluble fiber per 100 g is often the first choice. Often, it is started in small amounts to stimulate oral motor development. As intestinal rehabilitation continues, other solid feeds are introduced dictated by stool output. The pattern of introduction in solid feeds is often different than in normal infant feeding. Oftentimes, fiber-rich vegetables are first introduced in small quantities. Green beans have been suggested to decrease stool output in short gut syndrome [29]. Rather than the introduction of fruits which contain varying amounts of simple sugars, proteins are often added next. Finally, simple sugars can be introduced in small quantities. Oftentimes, lactose continues to be avoided due to the relative lactase deficiency that occurs with short or dysfunctional intestine.

Parenteral Nutrition Therapy

As the definition of intestinal failure implies, parenteral nutrition forms the foundation of nutritional supportive therapy. Many aspects of parenteral nutrition, especially early in the course of intestinal failure, conform to the practice of parenteral nutrition administration of any patient. As the diagnosis

of intestinal failure develops, differences unfold, especially pertaining to the prevention and/or treatment of parenteral nutrition associated liver disease.

Fluid and Electrolyte Management

The provision of sufficient fluid and electrolytes to maintain homeostasis is paramount throughout the course of therapy for intestinal failure. Fluid management must account for the basal metabolic expenditure of the patient as well as ongoing losses primarily in the form of stool or ostomy output. The basal metabolic fluid needs of a patient are directly related to the energy expended during normal physiologic activities [30] and are often estimated using body weight (Holiday-Segar Method) or body surface area. Ongoing gastrointestinal losses can be easily calculated when being collected in the form of ostomy output, though proves much more difficult when stool is assessed, often mixed with urine. An initial estimate of stool:fluid replacement ratio of 1:1 is a common starting point. It is important to realize that both maintenance and replacement requirements are estimates and must be continually monitored until an appropriate balance is acquired. Additional fluids may be required during the replacement of a deficit from periods of increased output or metabolic needs. Fluids are often managed through TPN to provide the maintenance rate, while additional IVF are given to replace output. When output stabilizes, replacement fluid can be added to the overall TPN mixture.

Similar to fluid requirements, electrolytes must account for insensible losses found in sweat and urine as well as that in stool [30] with sodium requirements approaching 3 mEq/kg/day in infants and potassium requirements approximately 2 mEq/kg/day. In general, the ability to keep stool/ostomy losses to less than 40 mL/kg/day can prevent electrolyte disturbances [26]. However, in practice the source of the output (gastrostomy, jejunostomy, ileostomy, colon) as well as the overall secretory/absorptive capacity of the remaining intestine is a major effecter of electrolyte losses thereby dictating replacement. It is not uncommon for children with high output stomas to approach 5–6 mEq/kg/day of sodium or more. The increased need for sodium in patients with ileostomies, for example, is well documented [31] and may have implications well beyond acute electrolyte management as depletion has been suggested to lead to poor weight gain and acidosis [32]. Hypomagnesemia has also been described as a common complication of high output stomas [33] and must be monitored closely as it can also lead to refractory hypocalcemia likely due to impaired parathyroid function [34]. Acidosis is a common concern due to bicarbonate loss in the stool, especially in infants with proximal stomas. Addition of acetate as an additional anion is often considered when designing TPN in infants with intestinal failure. Defining whether there is a normal anion gap (stool losses) or high anion gap due to an exogenous acid production such as L-lactate in dehydration or D-lactate with small bowel bacterial overgrowth [35] can be helpful when deciding on whether or not acetate will be required to maintain electrolyte homeostasis. As intestinal rehabilitation progresses and output slowly declines, a careful periodic assessment of electrolytes is essential as the cessation of TPN therapy will also lead to the discontinuation of electrolytes and potential electrolyte abnormalities if supplementation is required, but not considered.

Vitamins and Trace Elements

Vitamins and trace elements commonly referred to as micronutrients, play an important role in the management of intestinal failure. Deficiencies of one or more micronutrients are common in patients with intestinal failure while on parenteral nutrition and thereafter [36]. Fortunately, both water soluble and lipid soluble vitamins for parenteral nutrition are available in a pre-mixed form and in most cases provide adequate levels when administered daily [37]. Shortages in vitamins have at times led to the

practice of intermittent dosing out of necessity (three times weekly) with some suggestion of subclinical but important deficiencies (including vitamin C) occurring in adult patients [38]. Furthermore, in the absence of multivitamin administration, specific abnormalities, such as thiamine deficiency have been described [39]. Due to light-sensitivity, vitamins must be added separately to TPN admixtures on a daily basis to retain potency. When receiving parenteral nutrition chronically and as the sole source of nutrition, administration of vitamins is essential. As enteral feeds increase, parenteral vitamins can continue to be important in certain situations such as ileal resection (vitamin B12), fat malabsorption, or cholestasis (vitamins ADEK) until alternative methods of enteral delivery are achieved.

Trace elements, similar to multivitamins are also given in combination and include zinc, chromium, manganese, and copper. In patients with large gastrointestinal losses, zinc losses can be significant necessitating replacement. The ability to measure body stores of zinc is somewhat controversial as standard serum zinc levels only measure albumin bound zinc [26]. As copper homeostasis is maintained *via* biliary excretion and can accumulate in cholestatic liver disease, it is often decreased or omitted in parenteral nutrition as a hepatoprotective measure despite the risk of deficiency [26, 40]. Monitoring of copper levels in cholestatic infants receiving standard amounts (20 mcg/kg/day) has not been shown to lead to worsening liver disease or toxicity [41]. Manganese and chromium can also accumulate in patients on long term TPN necessitating removal or reduction in TPN. They also are often found in trace amounts in standard parenteral fluid preparation [42, 43]. Selenium, not found in standard pediatric trace element preparations, is also an essential trace element and deficiency has been described in infants on TPN [44]. Carnitine is a conditionally essential amino acid and is often found in decreased levels in preterm infants that are parenterally fed. Carnitine plays a role in the oxidation of long chain fatty acids and is therefore thought to play a role in the utilization of energy, especially from lipids [45]. While clear evidence of the utility of carnitine supplementation is lacking, it is often supplemented in parenteral nutrition, especially when it is the sole source of nutrition. In summary, despite a clear understanding of the role of the multiple trace elements added in parenteral nutrition with regard to deficiencies, toxicity, or in some cases, accurate measurement, there is enough of a concern that routine periodic monitoring of trace elements should be strongly considered in patients on TPN.

Conspicuously absent in parenteral nutrition formulations is iron due to an increased risk of adverse reactions to intravenous preparations. Consequently iron deficiency is a common problem in patients with intestinal failure in both children [36] and adults [46]. Fortunately, iron is absorbed primarily in the proximal intestinal tract increasing the likelihood for absorption if given through the enteral route. As long as patients are receiving minimal enteral feeds, enteral iron preparations should be considered as tolerated. In those in which oral administration cannot be achieved, the intravenous route can be considered.

Glucose

Glucose is a primary source of energy in parenteral nutrition. The utilization of glucose is dependent on its oxidation and exceeding this capacity can lead to inefficient use of glucose. Higher glucose infusion rates in parenterally fed children have been demonstrated to increase basal metabolic rate and respiratory quotient, leading to less energy available for protein synthesis and growth [47]. High plasma glucose concentrations can lead to hyperinsulinemia stimulating hepatic lipogenesis and acylglycerol formation while inhibiting fatty acid oxidation leading to hepatic steatosis [48]. However, hyperinsulinemia does not appear to be a uniform response and some patients appear to have a lower insulin secretory response, which may in fact contribute to hyperglycemia [49]. Glucose that exceeds the ability to be taken up by cells will ultimately have an osmotic diuretic effect, predisposing to glucosuria and dehydration. Thus, despite its importance in the provision of energy, care must be taken not to

Table 12.1 Nutritional factors influencing hepatotoxicity in intestinal failure therapy

Nutrient	Effect
Enteral feeds	Reduction of the need for TPN
	Enhancement of intestinal mucosa function
Glucose	High glucose infusion rate—hyperinsulinemia
	Hepatic lipogenesis
	Decreased fatty acid oxidation
Amino acids	Deficiency—hepatic steatosis
	Excess—hepatic cholestasis
Lipids	(Omega—6 fatty acids)
	Pro-inflammatory cytokine derivatives
	Phytosterol accumulation
	Loss of bile acid efflux (bile salt export pump)
	Loss of bile acid synthesis regulation
Trace elements	
Copper	Accumulation in cholestatic liver
Carnitine	Decreased fatty acid oxidation (hypothetical)

exceed the limits of usefulness. Most often a glucose infusion rate of 15–16 mg/kg/min is considered a maximum for infants.

In patients on chronic TPN therapy, there is often a balancing act between providing the essential calories needed for growth at glucose infusion rates to provide optimal utilization and cycling the TPN. TPN cycling can reduce insulin levels and potentially reduce liver dysfunction [40, 48] as well as serve psychological benefit to patients and their families from being disconnected for part of the day. While abrupt cessation of TPN has been associated with a reactive hypoglycemia, the effect is not uniform in all patients. Patients under the age of 3 years old do appear to be more susceptible [50] leading to tapering regimens which can allow cycling to occur. When establishing a cycling regimen, serial blood glucose measurements can be used to assess for the presence of hypoglycemia.

Protein

Infants with intestinal failure, similar to all patients on parenteral nutrition require sufficient amino acids to promote an anabolic state. In the preterm infant protein requirements approach 3–4 g/kg/day while older infants require 2–3 g/kg/day [51]. Addition of cysteine (40 mg/g) is recommended for children under 1 year of age as it is conditionally essential. Nonprotein calorie:nitrogen ratios in the range of 150 kcal/g N appear to provide optimal utilization of amino acids for protein production. Infants with short gut syndrome or intestinal dysfunction may have a component of a protein losing enteropathy thereby increasing amino acid needs. Most often, serum albumin measurements are used as a surrogate for assessment of protein needs.

Lipids

Lipids, like glucose, are a primary source of energy in parenteral nutrition therapy. While a very efficient source of calories, administration of soy-based lipid emulsions have been associated with the development of parenteral nutrition induced cholestasis. Cholestasis in infants with intestinal failure is a clear predictor of poor outcome [4] and multiple nutritional measures are often employed in an attempt to minimize hepatotoxicity (Table 12.1). Current theory as to how lipids lead to cholestasis

have focused on both the pro-inflammatory effects of omega-6 fatty acid derivatives and more commonly, the role of phytosterols [52, 53] which are also present in soy-based lipid preparations. By virtue of their structural similarity to native bile acids, phytosterols have been shown in vitro and in animal models to inhibit the bile acid nuclear receptor FXR [54] leading to unregulated uptake of bile acids into hepatocytes while decreasing hepatic clearance through the bile salt export pump.

To address this potential complication of parenteral nutrition therapy, two strategies have evolved: (1) the minimization of lipid therapy [55] or the provision of less soy-based lipid emulsion to decrease the overall exposure to phytosterols, and (2) the use of alternative lipid sources such as fish-oil-based emulsions [56] or a balance of several different lipid sources [57]. While these alternative products are not yet approved in the United States for use, they are gaining an increased popularity through investigative protocol.

Conclusion

The role of nutrition therapy in the management of intestinal failure is a critical part of overall management strategies to maintain homeostasis and growth while on parenteral nutrition and beyond. It is designed with the overall goal of rehabilitation and/or support in mind and is tailored according to physiological limitations and needs. The chronicity of parenteral nutrition administration, the therapeutic benefits of enteral feeds, and the constant assessment for the development of complications make it somewhat unique in the nutritional management of infants. Taking these aspects into consideration can make the management of intestinal failure rewarding and greatly improve the lives of patients with this devastating, chronic illness.

References

1. Thompson JS. Overview of etiology and management of intestinal failure. Gastroenterology. 2006;130(2 Suppl 1): S3–4.
2. Nucci A, Burns RC, Armah T, et al. Interdisciplinary management of pediatric intestinal failure: a 10-year review of rehabilitation and transplantation. J Gastrointest Surg. 2008;12(3):429–35. discussion 435–426.
3. Goulet O, Baglin-Gobet S, Talbotec C, et al. Outcome and long-term growth after extensive small bowel resection in the neonatal period: a survey of 87 children. Eur J Pediatr Surg. 2005;15(2):95–101.
4. Quiros-Tejeira RE, Ament ME, Reyen L, et al. Long-term parenteral nutritional support and intestinal adaptation in children with short bowel syndrome: a 25-year experience. J Pediatr. 2004;145(2):157–63.
5. Sherry B, Mei Z, Grummer-Strawn L, Dietz WH. Evaluation of and recommendations for growth references for very low birth weight (< or =1500 grams) infants in the United States. Pediatrics. 2003;111(4 Pt 1):750–8.
6. Cronk C, Crocker AC, Pueschel SM, et al. Growth charts for children with Down syndrome: 1 month to 18 years of age. Pediatrics. 1988;81(1):102–10.
7. Dalieri M, Fabeiro M, Prozzi M, et al. Growth assessment of children with neonatal short bowel syndrome (SBS). Nutr Hosp. 2007;22(4):455–60.
8. Olieman JF, Penning C, Spoel M, et al. Long-term impact of infantile short bowel syndrome on nutritional status and growth. Br J Nutr. 2011;15:1–9.
9. Williamson RC, Buchholtz TW, Malt RA. Humoral stimulation of cell proliferation in small bowel after transection and resection in rats. Gastroenterology. 1978;75(2):249–54.
10. Sigalet DL, Martin GR, Butzner JD, Buret A, Meddings JB. A pilot study of the use of epidermal growth factor in pediatric short bowel syndrome. J Pediatr Surg. 2005;40(5):763–8.
11. Byrne TA, Morrissey TB, Nattakom TV, Ziegler TR, Wilmore DW. Growth hormone, glutamine, and a modified diet enhance nutrient absorption in patients with severe short bowel syndrome. JPEN J Parenter Enteral Nutr. 1995;19(4):296–302.
12. Scolapio JS. Effect of growth hormone, glutamine, and diet on body composition in short bowel syndrome: a randomized, controlled study. JPEN J Parenter Enteral Nutr. 1999;23(6):309–12. discussion 312–303.

13. Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut. 2011;60(7):902–14.
14. Orenstein SR. Enteral versus parenteral therapy for intractable diarrhea of infancy: a prospective, randomized trial. J Pediatr. 1986;109(2):277–86.
15. Javid PJ, Collier S, Richardson D, et al. The role of enteral nutrition in the reversal of parenteral nutrition-associated liver dysfunction in infants. J Pediatr Surg. 2005;40(6):1015–8.
16. Joly F, Dray X, Corcos O, Barbot L, Kapel N, Messing B. Tube feeding improves intestinal absorption in short bowel syndrome patients. Gastroenterology. 2009;136(3):824–31.
17. Warner BB, Ryan AL, Seeger K, Leonard AC, Erwin CR, Warner BW. Ontogeny of salivary epidermal growth factor and necrotizing enterocolitis. J Pediatr. 2007;150(4):358–63.
18. Andorsky DJ, Lund DP, Lillehei CW, et al. Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. J Pediatr. 2001;139(1):27–33.
19. Dvorak B. Milk epidermal growth factor and gut protection. J Pediatr. 2010;156(2 Suppl):S31–5.
20. DiBaise JK, Young RJ, Vanderhoof JA. Intestinal rehabilitation and the short bowel syndrome: part 1. Am J Gastroenterol. 2004;99(7):1386–95.
21. Weser E, Babbitt J, Hoban M, Vandeventer A. Intestinal adaptation. Different growth responses to disaccharides compared with monosaccharides in rat small bowel. Gastroenterology. 1986;91(6):1521–7.
22. Vanderhoof JA, Grandjean CJ, Burkley KT, Antonson DL. Effect of casein versus casein hydrolysate on mucosal adaptation following massive bowel resection in infant rats. J Pediatr Gastroenterol Nutr. 1984;3(2):262–7.
23. Vanderhoof JA, Grandjean CJ, Kaufman SS, Burkley KT, Antonson DL. Effect of high percentage medium-chain triglyceride diet on mucosal adaptation following massive bowel resection in rats. JPEN J Parenter Enteral Nutr. 1984;8(6):685–9.
24. Bines J, Francis D, Hill D. Reducing parenteral requirement in children with short bowel syndrome: impact of an amino acid-based complete infant formula. J Pediatr Gastroenterol Nutr. 1998;26(2):123–8.
25. Crenn P, Morin MC, Joly F, Penven S, Thuillier F, Messing B. Net digestive absorption and adaptive hyperphagia in adult short bowel patients. Gut. 2004;53(9):1279–86.
26. Wessel JJ, Kocoshis SA. Nutritional management of infants with short bowel syndrome. Semin Perinatol. 2007;31(2):104–11.
27. Miller AJ. The neurobiology of swallowing and dysphagia. Dev Disabil Res Rev. 2008;14(2):77–86.
28. Olieman JF, Penning C, Ijsselstijn H, et al. Enteral nutrition in children with short-bowel syndrome: current evidence and recommendations for the clinician. J Am Diet Assoc. 2010;110(3):420–6.
29. Drenckpohl D, Hocker J, Shareef M, Vegunta R, Colgan C. Adding dietary green beans resolves the diarrhea associated with bowel surgery in neonates: a case study. Nutr Clin Pract. 2005;20(6):674–7.
30. Hellerstein S. Fluid and electrolytes: clinical aspects. Pediatr Rev. 1993;14(3):103–15.
31. Schwarz KB, Ternberg JL, Bell MJ, Keating JP. Sodium needs of infants and children with ileostomy. J Pediatr. 1983;102(4):509–13.
32. Bower TR, Pringle KC, Soper RT. Sodium deficit causing decreased weight gain and metabolic acidosis in infants with ileostomy. J Pediatr Surg. 1988;23(6):567–72.
33. Baker ML, Williams RN, Nightingale JM. Causes and management of a high-output stoma. Colorectal Dis. 2011;13(2):191–7.
34. Suh SM, Tashjian Jr AH, Matsuo N, Parkinson DK, Fraser D. Pathogenesis of hypocalcemia in primary hypomagnesemia: normal end-organ responsiveness to parathyroid hormone, impaired parathyroid gland function. J Clin Invest. 1973;52(1):153–60.
35. Perlmutter DH, Boyle JT, Campos JM, Egler JM, Watkins JB. D-Lactic acidosis in children: an unusual metabolic complication of small bowel resection. J Pediatr. 1983;102(2):234–8.
36. Yang CF, Duro D, Zurakowski D, Lee M, Jaksic T, Duggan C. High prevalence of multiple micronutrient deficiencies in children with intestinal failure: a longitudinal study. J Pediatr. 2011;159(1):39–44. e31.
37. Greene HL, Hambidge KM, Schanler R, Tsang RC. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition. Am J Clin Nutr. 1988;48(5):1324–42.
38. Mikalunas V, Fitzgerald K, Rubin H, McCarthy R, Craig RM. Abnormal vitamin levels in patients receiving home total parenteral nutrition. J Clin Gastroenterol. 2001;33(5):393–6.
39. Muwakkit S, Al-Aridi C, Saab R, Hourani R, Yazbeck N, Abboud M. Wernicke's encephalopathy during total parenteral nutrition in a child with acute lymphoblastic leukemia and acute pancreatitis. Neuropediatrics. 2009;40(5):249–51.
40. Slicker J, Vermilyea S. Pediatric parenteral nutrition: putting the microscope on macronutrients and micronutrients. Nutr Clin Pract. 2009;24(4):481–6.

41. Frem J, Sarson Y, Sternberg T, Cole CR. Copper supplementation in parenteral nutrition of cholestatic infants. J Pediatr Gastroenterol Nutr. 2010;50(6):650–4.
42. Moukarzel A. Chromium in parenteral nutrition: too little or too much? Gastroenterology. 2009;137(5 Suppl):S18–28.
43. Hardy G. Manganese in parenteral nutrition: who, when, and why should we supplement? Gastroenterology. 2009;137(5 Suppl):S29–35.
44. Masumoto K, Nagata K, Higashi M, et al. Clinical features of selenium deficiency in infants receiving long-term nutritional support. Nutrition. 2007;23(11–12):782–7.
45. Cairns PA, Stalker DJ. Carnitine supplementation of parenterally fed neonates. *Cochrane Database Syst Rev.* 2000;(4):CD000950.
46. Khaodhiar L, Keane-Ellison M, Tawa NE, Thibault A, Burke PA, Bistrian BR. Iron deficiency anemia in patients receiving home total parenteral nutrition. JPEN J Parenter Enteral Nutr. 2002;26(2):114–9.
47. Nose O, Tipton JR, Ament ME, Yabuuchi H. Effect of the energy source on changes in energy expenditure, respiratory quotient, and nitrogen balance during total parenteral nutrition in children. Pediatr Res. 1987;21(6):538–41.
48. Lloyd DA, Gabe SM. Managing liver dysfunction in parenteral nutrition. Proc Nutr Soc. 2007;66(4):530–8.
49. Beltrand J, Colomb V, Marinier E, et al. Lower insulin secretory response to glucose induced by artificial nutrition in children: prolonged and total parenteral nutrition. Pediatr Res. 2007;62(5):624–9.
50. Bendorf K, Friesen CA, Roberts CC. Glucose response to discontinuation of parenteral nutrition in patients less than 3 years of age. JPEN J Parenter Enteral Nutr. 1996;20(2):120–2.
51. Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. JPEN J Parenter Enteral Nutr. 2004;28(6):S39–70.
52. Iyer KR, Spitz L, Clayton P. BAPS prize lecture: New insight into mechanisms of parenteral nutrition-associated cholestasis: role of plant sterols. British Association of Paediatric Surgeons. J Pediatr Surg. 1998;33(1):1–6.
53. Clayton PT, Whitfield P, Iyer K. The role of phytosterols in the pathogenesis of liver complications of pediatric parenteral nutrition. Nutrition. 1998;14(1):158–64.
54. Carter BA, Taylor OA, Prendergast DR, et al. Stigmasterol, a soy lipid-derived phytosterol, is an antagonist of the bile acid nuclear receptor FXR. Pediatr Res. 2007;62(3):301–6.
55. Cober MP, Teitelbaum DH. Prevention of parenteral nutrition-associated liver disease: lipid minimization. Curr Opin Organ Transplant. 2010;15(3):330–3.
56. Puder M, Valim C, Meisel JA, et al. Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. Ann Surg. 2009;250(3):395–402.
57. Goulet O, Joly F, Corriol O, Colomb-Jung V. Some new insights in intestinal failure-associated liver disease. Curr Opin Organ Transplant. 2009;14(3):256–61.

Chapter 13
Hormone Therapy to Improve Growth in Infants with Chronic Kidney Disease

Natalia Mejía-Gaviria, Flor Ángel Ordoñez, and Fernando Santos

Key Points

- Growth retardation in infants with CKD is secondary to malnutrition and/or low birth weight in the vast majority of cases.
- Nutritional assessment of children with CKD should be promptly initiated in order to control uremic symptoms, prevent renal bone disease, and assure optimum growth.
- Forced nutrition by enteral or parenteral feeding may be necessary to ensure nutritional goals.
- In infants whose growth retardation persists despite a good metabolic and nutritional control, therapy with rhGH must be considered early.
- Therapy with rhGH improves longitudinal growth with no undesirable effects on bone maturation, renal failure progression, or metabolic control.

Keywords Malnutrition • Growth • Growth hormone • Catch-up growth • Chronic kidney disease • Nutritional supplementation • Low birth weight • Growth retardation

Definition and Stages of Chronic Kidney Disease

The term chronic kidney disease (CKD) denotes the persistence of a renal disorder for at least 3 months. CKD is graded as stage 1 when renal glomerular filtration rate (GFR) is normal and from stages 2–5 when the GFR is low and according to the severity of the GFR reduction [1]. Stage 5 CKD equals the classic term "end-stage renal disease" (ESRD) and implies the need of dialysis. The application of this classification to infants needs to take into account that the GFR, expressed in mL/min/1.73 m^2, gradually increase during the first months of life and does not reach normal adult values until 1 year of age. In this chapter, CKD will refer to stages with decreased GFR unless the opposite is specifically mentioned.

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Epidemiological Data on Growth Retardation in CKD

Growth retardation is still a major manifestation of CKD when it occurs in the pediatric age and an important problem in the management of these patients because the failure to achieve a normal adult height accounts for a permanent sequelae and it is a serious obstacle to the complete social rehabilitation of these individuals. Even for those patients able to grow within the normal reference percentiles, the presence of CKD makes difficult the attainment of the target height as predicted by parental heights.

Recent data from collaborative registries indicate that the height of children with CKD stands below the lower limit of normal reference values in approximately one third and is above the 50th percentile in less than 20% of patients [2]. Following diagnosis, growth retardation only consistently improves in the group of patients aged 0–1 year but not in older children.

Pathogenic Factors of Growth Retardation in CKD

Many factors may be responsible for the impairment of growth in CKD. Thus, metabolic acidosis, fluid and electrolyte abnormalities including hypovolemia and sodium deficit, persistent anemia, bone mineral disorder, reduced food intake, protein hypercatabolism, alterations of growth hormone metabolism, chronic inflammation, low intratuterine growth, retention of uremic toxins, etc. all may adversely interfere with a normal growth in a child with CKD [3]. Some of these factors, such as anemia, acid–base disturbance, sodium deficit, osseous deformities, can nowadays be adequately prevented and treated and, in spite of that, growth retardation often persists in these children. Therefore, we will focus on the protein-energy wasting syndrome [4], the resistance to growth hormone (GH) and the inability to exhibit postnatal catch-up as the main mechanisms leading to subnormal growth in CKD.

In CKD the coexistence of normal circulating values of GH and the acceleration of growth rate caused by high doses of exogenous GH support the assumption that renal failure causes partial resistance to the action of GH. The Fig. 13.1 graphically summarizes the abnormalities in GH—insulin-like growth factor I (IGF-I) metabolism found in animals and humans with CKD [5]. Within these alterations, the following ones might likely have a significant role in the genesis of GH resistance: (1) disturbed serum GH profile with reduced amplitude of secretory peaks [6]; (2) depressed expression of GH receptor in liver and growth cartilage [7–9]; (3) low circulating values of free IGF-I [10, 11]; (4) postreceptorial defect in the intracellular signaling pathway of GH [12, 13]. Malnutrition and chronic inflammation may also be responsible for GH resistance and may explain in part, but not completely, some of these alterations, emphasizing the complex interplay of these factors in the genesis of growth failure in the uremic state.

The prevalence of low birth size is much higher in children with congenital CKD than in the normal population. Approximately 39 and 29% of newborns with congenital CKD have been found to be preterm or small for gestational age (SGA), respectively, in comparison with 8% in the reference population [14].

Specific Role of Nutrition and Why and How Nutrition Is Impaired in CKD

Goals of pediatric renal nutrition therapy include maintenance of adequate intake for optimal macro and micronutrient status, optimization of growth, prevention of uremic toxicity as well as of metabolic disturbances and mineral and bone disease, improvement of the quality of life and survival, and reduction

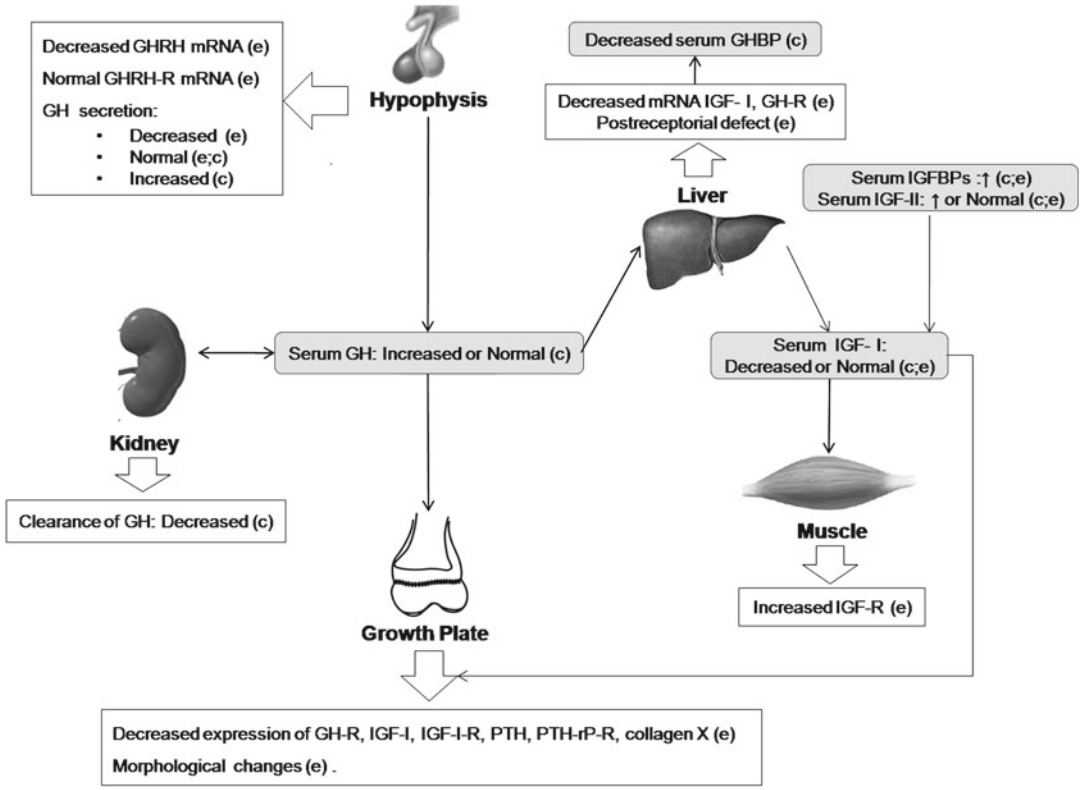

Fig. 13.1 Alterations of growth hormone (GH) and insulin-like growth factor (IGF)-I metabolism in chronic renal failure found in clinical (c) and experimental studies (e). *Upward arrow* Increased; *IGFBPs* IGF binding proteins; *GHRH* GH releasing hormone; *mRNA* messenger ribonucleic acid; *R* receptor; *GHBP* GH binding protein; *PTH* parathyroid hormone; *PTHrP* PTH-related peptide

of the risk of chronic morbidities in adulthood. Several factors hamper the achievement of nutritional targets in infants with CKD. Low calorie and protein intake negatively impacts longitudinal length, catch-up growth, and neurological development [15] (Table 13.1.). Malnutrition is a serious and common complication in children with CKD. It is characterized by loss of fat tissue as a consequence of an inadequate or scarce diet with adaptive and protective mechanisms like hunger, diminution of energy expenditure, and preservation of lean body and muscle mass, at least in initial stages. Furthermore, protein-energy wasting (PEW) syndrome or its severe form, cachexia, comprises weight loose, underutilization of fat tissue, decreased protein stores, muscle wasting, and anorexia as a maladaptive response to elevated metabolic expenditure [16–18]. Cachexia/PEW syndrome has been implicated as risk factor for cardiovascular diseases and decreased life expectancy in adults and children with CKD [19, 20]. The restitution or adequacy of diet reverses malnutrition but this does not fully occur in cachexia/PEW in uremia [21].

The pathophysiology of cachexia/PEW in renal disease involves many aspects that interact with each other resulting in anorexia and muscle protein breakdown through activation of caspase 3 and the ubiquitin-proteasome system [22]. High serum levels of pro-inflammatory cytokines tumoral necrosis factor-α, interleukin-1β, and interleukin-6 as a result of impaired renal clearance [23], volume overload or oxidative stress, enhance muscle degradation and suppress appetite through hypothalamic pathways [24, 25]. Appetite-controlling hormones are dysregulated in uremia contributing to anorexia. Renal excretion of anorexigenic peptides such as leptin, insulin, obestatin, and alpha melanocyte

Table 13.1 Factors affecting nutritional goals in CKD

Poor appetite
Diet and fluid restrictions
Decreased intestinal absorption of nutrients
Recurrent vomiting
Distortion of taste and smell
Metabolic acidosis
Salt-wasting
Mineral and bone disorder—secondary hyperparathyroidism
Psychosocial issues and developmental delay
Anemia
Intercurrent diseases
Prescription of fasting because of surgery procedures
Polyuria or inability to concentrate urine
Medications interfering with food intake

stimulating hormone is impaired so abnormal high levels are found in malnourished patients likely contributing to decreased nutrient intake, while circulating concentrations of orexigenic peptides such as neuropeptide Y, agouti-related peptide, and active ghrelin, decrease [26–30]. Moreover, serum leptin levels correlate with plasma insulin concentrations, independent of body fat content, suggesting that elevated serum leptin may play a role in reducing glucose-stimulated insulin secretion and glucose intolerance in CKD [31]. Beyond its effects through the hypothalamus, leptin, and ghrelin indirectly modulate pro-inflammatory cytokines. Abnormalities in the growth plate structure and dynamics dependent and independent on malnutrition have been described in uremic rats [32].

Guidelines on Nutrition in Infants with CKD

Evaluation of nutritional and growth status: Includes clinical and biochemical parameters as well as a detailed history of specific markers of malnutrition (Table 13.2.). This assessment must be multidisciplinary and dietary counseling should be individualized and performed by a dietitian who ideally has expertise in renal and pediatric nutrition. Periodicity of visits is based on the age of the child and severity of CKD though infants with polyuria, growth delay, decreasing or low body mass index (BMI) or recent acute changes in medical status or dietary intake need more frequent evaluation (Table 13.3.) [33].

Energy: Calorie intake requirements for infants with CKD are equivalent to 100% of estimated energy requirement (EER) for healthy children with the same chronological age adjusted to individual physical activity (Table 13.4.) [33]. Calories derived from glucose in the dialysate (8–12 kcal/kg per day) must be considered when calculating total energy intake in patients on peritoneal dialysis. For infants with CKD, breast milk is the most appropriate choice or whey-based infant formula with low renal solute load. Weaning can be introduced between 4 and 6 months. Expressed breast milk may be fortified with modular carbohydrate, fat and protein components or mixed with another formula. Additional nutritional supplementation by oral route must be considered if the child is not achieving expected rates of weight gain and/or growth for age, when the amount of milk is insufficient or if fluid restriction is desirable. At 1 year of age is advisable to continue with infant formula with personalized modifications instead of changing to cow's milk [34].

Table 13.2 Evaluation of nutritional status

Specific signs and symptoms	Biochemical parameters	Detailed history
PEW		
Change in appetite	Standard biochemistry	Age of onset of CKD
Gastrointestinal problems	Albumin	Etiology of CKD
Nausea	Prealbumin	Age at dialysis initiation
Vomiting	Serum creatinine	Acute or chronic inflammatory disorders comorbidities
Constipation	Creatinine kinetics	
Gastroesophageal reflux	Lymphocyte count	
Swallowing difficulties	Hemoglobin	
Fatigue		
Cachexia		
Thin hair		
Yellowish teeth lacking in enamel		
Pale tongue with scattered papillae		
Pale skin		
Smelly breath		

Modified from ref. [50]
PEW protein-energy wasting syndrome

Table 13.3 Periodicity of evaluation of growth and nutritional status in infants with CKD stages 2–5

	Minimum interval (months)				
	Age: 0 to <1 year		Age: 1–3 years		
	Stages of CKD		Stages of CKD		
Measure	2–4	5	2–3	4–5	5
Dietary intake (3-day diet record or three 24-h dietary recall)	0.5–3	0.5–2	1–3	1–3	1–3
Estimated dry weight and weight for age percentile or SDS	0.5–1.5	0.25–1	1–3	1–2	0.2–1
Length or height for age percentile or SDS	0.5–1.5	0.5–1	1–3	1–2	1
BMI for height age percentile or SDS	0.5–1.5	0.5–1	1–3	1–2	1
Head circumference for age percentile or SDS	0.5–1.5	0.5–1	1–3	1–2	1–2
Height or length velocity-for-age percentile or SDS	0.5–2	0.5–1	1–6	1–3	1–2

BMI body mass index; *SDS* standard deviation score
Modified from ref. [33]

Protein: Dietary protein intake should be maintained at 100–140% of the Dietary Reference Intake [34] (DRI) for ideal body weight in children with CKD stage 3 and at 100–120% of the DRI in children with CKD stages 4–5 [33]. Additional protein increment must be provided, based on anticipated peritoneal loses ranging from 0.15 to 0.35 mg/kg and 0.1 g/kg/day for children on hemodialysis (Table 13.4.). Special carefulness must be taken on quality and bioavailability of the protein resources given the indirect link between phosphorus and cardiovascular morbidity in children. When protein requirements are assessed is imperative to ensure caloric needs previously to avoid increased generation of urea.

Sodium chloride: Infants with CKD especially those with renal dysplasia may have polyuria and urinary salt-wasting which contribute to severe height deficits. When sodium chloride excretion exceeds the intake form standard formula o breast milk, supplement of 4–7 mmol/kg/day of salt may be required with close monitoring of blood pressure [35].

Table 13.4 Recommended caloric and protein intake for children with CKD

CKD stage and patient's age	Energy (kcal/kg/day)	Protein (g/kg/day)
CKD 3		
0–6 months	115–150	1.5–2.1
7–12 months	95–150	1.2–1.7
1–3 years	95–120	1.05–1.5
CKD 4–5		
0–6 months	115–150	1.5–1.8
7–12 months	95–150	1.2–1.5
1–3 years	95–120	1.05–1.25
Peritoneal dialysis		
0–6 months	115–150	1.8
7–12 months	95–150	1.5
1–3 years	95–120	1.3
Hemodialysis		
0–6 months	115–150	1.6
7–12 months	95–150	1.3
1–3 years	95–120	1.15

Modified from refs. [33] and [34]

Table 13.5 Recommended calcium and phosphorus intake for children with CKD stages 2–5

	Recommended calcium intake (mg elemental Ca)		Recommended phosphorus intake (mg/dL)	
Patient's age	DRI (100%)	Upper limit diet + phosphate binders	Normal P + high PTH (DRI ≤100%)	High P + high PTH (DRI ≤80%)
0–6 months	210	≤420	100	≤80
7–12 months	270	≤540	275	≤220
1–3 years	500	≤1,000	460	≤370

DRI dietary reference intake; *PTH* parathyroid hormone
Modified from reference KDOQI Work Group [33]

Vitamin and trace element: Infants with CKD should receive at least 100% of the DRI for thiamin (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B8), cobalamin (B12), ascorbic acid (C), retinol (A), alpha-tocopherol (E), vitamin K, folic acid, copper, and zinc [33]. Supplements of water-soluble vitamins are indicated in children on dialysis who are not receiving nutritional supplements [35].

Calcium and phosphate: Balance of mineral homeostasis must be adjusted to achieve good skeletal development without promoting vascular calcifications. The total calcium intake from diet and calcium-based phosphate binders in children with CKD stages 2–5 should be in the range of 100–200% of the DRI for age [33] (Table 13.5.). If an insufficient calcium intake is detected, consumption of food with high endogenous calcium content like milk, cheese, broccoli, and calcium-fortified food products must be recommended. In all CKD stages, it is suggested to avoid serum phosphorus concentrations both above and below the normal reference range for age since highs levels aggravate secondary hyperparathyroidism and low levels can worse osteomalacia. Moderate phosphate restriction prevents and improves secondary hyperparathyroidism with a safe profile in respect to growth, nutrition, and bone mineralization. In children with CKD stages 3–5 with serum parathyroid hormone (PTH) concentration above the target range for CKD stage and serum phosphorus concentration is within the normal reference range for age, a dietary phosphorus intake to 100% of the DRI for age is suggested. In children with CKD stages 3–5 with increased serum phosphorus levels for age and PTH concentrations above the target range for CKD stage, a reduction in dietary phosphorus intake to 80%

of the DRI for age is advisable (Table 13.5) [33]. To accomplish this objective, protein sources with low phosphorus content should be prescribed. In young infants, whose major source of protein and phosphorus came from milk and dairy products, metabolic control can be achieved using oral and/or enteral formulas with low phosphorus content and delaying the introduction of cow's milk until the age of 18–36 months [33].

Response of Growth to Forced Nutrition in Infants

It has been described that energy intake less than 80% of the DRI may produce growth delay. Restoring calories to 100% of estimated average requirement (EAR) allows catch-up growth in infants <2 years [36, 37]. Exceeding amount of calories beyond this point has not shown further improvement in length and can lead to overweight. Clinical studies have shown the benefits of forced nutrition in children with renal disease. Honda et al. [38] described 15 infants on peritoneal dialysis whose mean growth velocity indexes were positively correlated to energy but not protein intake. Similar findings were described by other study before and 1 year after therapy with growth hormone in prepuberal children on dialysis [39]. Energy-dense diet and commercial nutritional supplements can be given by oral route, however in infants difficulties in feeding often arise. Refusal to eat, vomiting, and spontaneous decreased intake are frequent, so dietary requirements cannot be maintained consistently with oral feeding. In those cases enteral (nasogastric, nasojejunal, gastrostomy, or gastro-jejunostomy) or parenteral nutrition may be necessary to ensure nutritionals objectives. Ledderman et al. found achievement of catch-up growth in infants whose calorie requirements were fulfilled with nasogastric tube and gastrostomy for long term. Better control of secondary hyperparathyroidism was found as enteral feeding continued, regardless of mineral-bone disease standard treatment [37]. Previous report on children with CKD highlighted the importance of caloric intake, PTH, and blood urea nitrogen levels on growth retardation [40]. Other approaches like intradialytic parenteral nutrition were capable of reversing weight loss and improve BMI in children on hemodialysis [41], although other group described slightly or no changes in serum albumin, as a surrogate marker of survival on CKD [42].

Use of Growth Hormone in Infants with CKD: Rationale and Indications

Although acknowledging the need for optimal nutritional management to optimize growth of infants with CKD, height deficit cannot always be overcome despite aggressive supplemental feeding in these patients, as disclosed by a detailed analysis of published series in which forced feeding did not invariably result in catch-up growth [36, 43–45]. On the other hand, as mentioned above, the prevalence of low birth size is much higher in children with congenital CKD than in the normal population. Therefore, infants with CKD not only need to have a normal growth rate but to undergo a longitudinal catch-up growth during the first months of life. Most of low birth weight infants without associated chronic diseases have postnatal growth sufficient to normalize height in the first 2 years of life [46]. Even a moderate reduction of renal function may prevent this early catch-up growth in CKD patients. This adverse effect of CKD on infants' growth is consistent with the typical growth pattern described for pediatric patients with CKD [47]. The patient's height separates from normal reference percentiles during infancy and puberty. Between these two periods the patient is able to keep a "normal" growth rate so that the height deficit does not become relatively greater, particularly if the patient's CKD stage is not advanced.

Thus, to avoid the aggravation of growth deficit during the infancy period, infants with CKD not associated with other growth inhibiting diseases, such as bone dysplasias, congenital malformations,

endocrine disorders, etc., in whom growth retardation persists in the presence of a good metabolic and nutritional control should be treated with GH. In this group of patients, administration of recombinant human GH (rhGH) at doses of 0.33 mg/kg/week injected daily by subcutaneous route has been shown to improve longitudinal growth with no undesirable effects on bone maturation, renal failure progression, or metabolic control [48]. Therapy with rhGH should be withdrawn once the child attains the mid-parental height. From this point on, if the renal failure is not advanced the patient may be able to keep a normal growth velocity during the childhood and so keep the genetically determined percentile for height. At the time of puberty, rhGH treatment may again be required in order to achieve a normal growth spurt. Patients with severe degrees of CKD are usually not only unable to exhibit catch-up growth but also to keep a "normal" growth rate. In these patients, maintained administration of rhGH is necessary to avoid the fall of the height below the percentile that corresponds to the mid-parental height. In these cases, it should be kept in mind that the best response to rhGH, i.e. the maximal acceleration of growth velocity, is habitually observed during the first year of treatment and that prolonged therapy is often associated with poor compliance with therapy [49].

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). Kidney Int. 2009;76 Suppl 113:S1–130.
2. The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) 2008 annual report. https://web.emmes.com/study/ped/annlrept/annlrept.html. Accessed 8 September 2011.
3. Fine RN. Etiology and treatment of growth retardation in children with chronic kidney disease and end-stage renal disease: a historical perspective. Pediatr Nephrol. 2010;25:725–32.
4. Fouque D, Pelletier S, Mafra D, Chauveau P. Nutrition and chronic kidney disease. Kidney Int. 2011;80:348–57.
5. Garcia E, Rodriguez J, Santos F. Crecimiento y nutrición en el fallo renal crónico. In: Santos F, Garcia-Nieto V, Rodríguez-Iturbe B, editors. Nefrologia Pediatrica. 2nd ed. Madrid: Aula Medica; 2006. p. 683–93.
6. García E, Santos F, Rodríguez J, Martínez V, Rey C, Veldhuis J, et al. Impaired secretion of growth hormone in experimental uremia: relevance of caloric deficiency. Kidney Int. 1997;52:648–53.
7. Tönshoff B, Edén S, Weiser E, Carlsson B, Robinson IC, Blum WF, et al. Reduced hepatic growth hormone (GH) receptor gene expression and increased plasma GH binding protein in experimental uremia. Kidney Int. 1994;45:1085–92.
8. Martínez V, Balbín M, Ordóñez FA, Rodríguez J, García E, Medina A, et al. Hepatic expression of growth hormone receptor/binding protein and insulin-like growth factor I genes in uremic rats. Influence of nutritional deficit. Growth Horm IGF Res. 1999;9:61–8.
9. Edmondson SR, Baker NL, Oh J, Kovacs G, Werther GA, Mehls O. Growth hormone receptor abundance in tibial growth plates of uremic rats: GH/IGF-I treatment. Kidney Int. 2000;58:62–70.
10. Powell DR, Durham SK, Liu F, Baker BK, Lee PD, Watkins SL, et al. The insulin-like growth factor axis and growth in children with chronic renal failure: a report of the Southwest Pediatric Nephrology Study Group. J Clin Endocrinol Metab. 1998;83:1654–61.
11. Tönshoff B, Blum WF, Wingen AM, Mehls O. Serum insulin-like growth factors (IGFs) and IGF binding proteins 1, 2, and 3 in children with chronic renal failure: relationship to height and glomerular filtration rate. The European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. J Clin Endocrinol Metab. 1995;80:2684–91.
12. Schaefer F, Chen Y, Tsao T, Nouri P, Rabkin R. Impaired JAK-STAT signal transduction contributes to growth hormone resistance in chronic uremia. J Clin Invest. 2001;108:467–75.
13. Sun DF, Zheng Z, Tummala P, Oh J, Schaefer F, Rabkin R. Chronic uremia attenuates growth hormone-induced signal transduction in skeletal muscle. J Am Soc Nephrol. 2004;15:2630–6.
14. Franke D, Völker S, Haase S, Pavicic L, Querfeld U, Ehrich JH, et al. Prematurity, small for gestational age and perinatal parameters in children with congenital, hereditary and acquired chronic kidney disease. Nephrol Dial Transplant. 2010;25:3918–24.
15. Norman LJ, Macdonald IA, Watson AR. Optimising nutrition in chronic renal insufficiency-growth. Pediatr Nephrol. 2004;19:1245–52.
16. Mak RH, Ikizler AT, Kovesdy CP, Raj DS, Stenvinkel P, Kalantar-Zadeh K. Wasting in chronic kidney disease. J Cachex Sarcopenia Muscle. 2011;2:9–25.

17. Evans WJ, Morley JE, Argiles J, et al. Cachexia: a new definition. Clin Nutr. 2008;27:793–9.
18. Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73:391–8.
19. Rambod M, Bross R, Zitterkophet J, et al. Association of Malnutrition-Inflammation Score with quality of life and mortality in hemodialysis patients: a 5-year prospective cohort study. Am J Kidney Dis. 2009;53:298–309.
20. Wong CS, Hingorani S, Gillen DL, et al. Hypoalbuminemia and risk of death in pediatric patients with end-stage renal disease. Kidney Int. 2002;61:630–7.
21. Mak RH, Cheung W. Therapeutic strategy for cachexia in chronic kidney disease. Curr Opin Nephrol Hypertens. 2007;16:542–6.
22. Mitch WE. Proteolytic mechanisms, not malnutrition, cause loss of muscle mass in kidney failure. J Ren Nutr. 2006;16:208–11.
23. Pecoits-Filho R, Sylvestre LC, Stenvinkel P. Chronic kidney disease and inflammation in pediatric patients: from bench to playground. Pediatr Nephrol. 2005;20:714–20.
24. Cheung WW, Paik KH, Mak RH. Inflammation and cachexia in chronic kidney disease. Pediatr Nephrol. 2010;25(4):711–24.
25. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. Am J Clin Nutr. 2004;80:299–307.
26. Daschner M, Tonshoff B, Blum WF, et al. Inappropriate elevation of serum leptin levels in children with chronic renal failure. European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. J Am Soc Nephrol. 1998;9:1074–9.
27. Buscher AK, Buscher R, Hauffa BP, Hoyer PF. Alterations in appetite-regulating hormones influence protein-energy wasting in pediatric patients with chronic kidney disease. Pediatr Nephrol. 2010;25:2295–301.
28. Yoshimoto A, Mori K, Sugawara A, Mukoyama M, et al. Plasma ghrelin and desacyl ghrelin concentrations in renal failure. J Am Soc Nephrol. 2002;13:2748–52.
29. Nusken KD, Groschl M, Rauh M, Stohr W, Rascher W, Dotsch J. Effect of renal failure and dialysis on circulating ghrelin concentration in children. Nephrol Dial Transplant. 2004;19:2156–7.
30. Mak RH, Cheung W, Cone RD, Marks DL. Orexigenic and anorexigenic mechanisms in the control of nutrition in chronic kidney disease. Pediatr Nephrol. 2005;20:427–31.
31. Stenvinkel P, Heimburger O, Lonnqvist F. Serum leptin concentrations correlate to plasma insulin concentrations independent of body fat content in chronic renal failure. Nephrol Dial Transplant. 1997;12:1321–5.
32. Santos F, Carbajo-Perez E, Rodriguez J, et al. Alterations of the growth plate in chronic renal failure. Pediatr Nephrol. 2005;20:330–4.
33. KDOQI Work Group. KDOQI clinical practice guideline for nutrition in children with CKD: 2008 update. Executive summary. Am J Kidney Dis. 2009;53:S11–104.
34. Chronic Kidney Disease Guidelines. Available at http://www.cari.org.qu/ckd_nutrition_list_published.php. Cited 2012 Sep 26.
35. Pollock C, Voss D, Hodson E, Crompton C. The CARI guidelines. Nutrition and growth in kidney disease. Nephrology (Carlton). 2005;10 Suppl 5:S177–230.
36. Kari JA, Gonzalez C, Ledermann SE, Shaw V, Rees L. Outcome and growth of infants with severe chronic renal failure. Kidney Int. 2000;57:1681–7.
37. Ledermann SE, Shaw V, Trompeter RS. Long-term enteral nutrition in infants and young children with chronic renal failure. Pediatr Nephrol. 1999;13:870–5.
38. Honda M, Kamiyama Y, Kawamura K, et al. Growth, development and nutritional status in Japanese children under 2 years on continuous ambulatory peritoneal dialysis. Pediatr Nephrol. 1995;9:543–8.
39. Zadik Z, Frishberg Y, Drukkeret A, et al. Excessive dietary protein and suboptimal caloric intake have a negative effect on the growth of children with chronic renal disease before and during growth hormone therapy. Metabolism. 1998;47:264–8.
40. Claris-Appiani A, Bianchi ML, Biniet P, et al. Growth in young children with chronic renal failure. Pediatr Nephrol. 1989;3:301–4.
41. Orellana P, Juarez-Congelosi M, Goldstein SL. Intradialytic parenteral nutrition treatment and biochemical marker assessment for malnutrition in adolescent maintenance hemodialysis patients. J Ren Nutr. 2005;15:312–7.
42. Krause I, Shamir R, Davidovits M, et al. Intradialytic parenteral nutrition in malnourished children treated with hemodialysis. J Ren Nutr. 2002;12:55–9.
43. Parekh RS, Flynn JT, Smoyer WE, Milne JL, Kershaw DB, Bunchman TE, et al. Improved growth in young children with severe chronic renal insufficiency who use specified nutritional therapy. J Am Soc Nephrol. 2001;12:2418–26.
44. Abitbol CL, Zilleruelo G, Montane B, Strauss J. Growth of uremic infants on forced feeding regimens. Pediatr Nephrol. 1993;7:173–7.
45. Brewer ED. Growth of small children managed with chronic peritoneal dialysis and nasogastric tube feedings: 203-Month experience in 14 patients. Adv Perit Dial. 1990;6:269–72.

46. Argente J, Mehls O, Barrios V. Growth and body composition in very young SGA children. Pediatr Nephrol. 2010;25:679–85.
47. Karlberg J, Schaefer F, Hennicke M, Wingen AM, Rigden S, Mehls O. Early age-dependent growth impairment in chronic renal failure. European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. Pediatr Nephrol. 1996;10:283–7.
48. Santos F, Moreno ML, Neto A, et al. Improvement in growth after 1 year of growth hormone therapy in well-nourished infants with growth retardation secondary to chronic renal failure: results of a multicenter, controlled, randomized, open clinical trial. Clin J Am Soc Nephrol. 2010;5:1190–7.
49. Rosenfeld RG, Bakker B. Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. Endocr Pract. 2008;14:143–54.
50. Edefonti A, Mastrangelo A, Paglialonga F. Assessment and monitoring of nutrition status in pediatric peritoneal dialysis patients. Perit Dial Int. 2009;29 Suppl 2:S176–9.

Chapter 14
Nutrition of Infants and HIV

Lars T. Fadnes, Tanya Doherty, Debra Jackson, Ingunn Marie S. Engebretsen, and Ameena Goga

Key Points

- Appropriate infant feeding is essential for the health of all children
- For children of HIV-positive mothers there are some additional important issues. This includes
  - Use of antiretroviral drugs as prophylaxis or therapy to reduce HIV transmission
  - Questions related to duration of different feeding modalities
  - Questions related to feasibility and acceptability of the choices related to infant feeding and therapy
- The current guidelines from the World Health Organisation (WHO) on infant feeding in the context of HIV are in most aspects more similar to the recommendations for the general population than they were earlier with added emphasis on the importance of antiretroviral drugs

Keywords Infant Nutritional Physiological Phenomena • Breast Feeding • Infant Formula • HIV/HIV Infections • Highly Active Antiretroviral Therapy/HAART • Health Planning Guidelines

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Introduction

Since 1985, it has been known that HIV can be transmitted through breast milk [1]. Infants who are infected with HIV are at a high risk of early death and carry a heavy burden of disease [2–4]. If no actions are taken, around one third of the children will be infected during pregnancy (5–10%), delivery (10–20%), or breastfeeding (10–20%) [5].

Despite the risk of HIV infection via breast milk, avoidance of breastfeeding has been associated with substantial morbidity and mortality in many settings and in many of the settings where HIV is prevalent [6], which makes it necessary to balance these competing risks [7].

Current approaches to prevent postnatal HIV transmission through breastfeeding in resource-poor settings include the avoidance of all breastfeeding (exclusive replacement feeding) or breastfeeding together with antiretroviral drugs given to the infant (as prophylaxis) or to the mother (as either prophylaxis for the breastfeeding period or treatment depending on the mothers CD4 count).

Exclusive Breastfeeding

There is substantial evidence that exclusive breastfeeding (feeding an infant on breast milk alone with no other liquids or solid foods except for medicines and vitamin–mineral supplements) during the first half of infancy has substantial child survival benefits—even in the context of HIV [8–13]. Exclusive breastfeeding has been found to result in a marked decrease in HIV transmission compared to non-exclusive breastfeeding in several large studies in South Africa, Zimbabwe, Zambia, and Ivory Coast [8, 9, 11–13].

Early cessation of breastfeeding, at around 6 months of age, was previously recommended by the WHO as a strategy to limit the exposure to HIV through breast milk [14], but is no longer recommended since evidence from Zambia has shown that the benefits of continued breastfeeding far outweigh the child survival risk of early cessation in many settings [15]. Several studies from sub Saharan Africa have highlighted the dangers of early cessation of breastfeeding under conditions of underlying poor socio-economic status and food insecurity, as locally available foods often do not meet the nutritional needs of non-breastfed infants between 6 and 12 months of age [16, 17]. Furthermore, replacing breast milk with local foods would double the estimated daily cost of feeding 6–12-month-old infants [17].

Importance of Appropriate Complementary Feeding

During the last decade, the optimal duration of exclusive breastfeeding has received more attention, possibly at the expense of optimal complementary feeding [18]. However, there is extensive documentation that high quality complementary feeding after the first half of infancy is essential for optimal child health [19–23]. Furthermore, there are several reports that document that complementary feeding is often sub-optimal in many settings where HIV is prevalent [19]. A study in Zimbabwe found that among HIV-positive mothers with infants at around 6 months of age, the median energy intake was 1,382 kJ (54% of recommended daily intake of energy [RDI]) among weaned infants compared with 2,234 kJ (87% of RDI) among breastfeeding infants [17]. Food unavailability was the primary barrier to early weaning, suggesting that it is difficult for HIV-positive women in Zimbabwe to safely wean their infants from breast milk. There is a need to find strategies to improve this situation including provision of training and support to mothers and health professionals in proper complementary feeding, and improving food security [18, 24–26].

A Zambian study sought to answer the question of whether early weaning is safe in an African setting with a high background infant mortality rate [15]. The study randomized HIV-positive women

Box 14.1 WHO Guidelines on HIV and Infant Feeding 2010

Recommendation 1

Ensuring mothers receive the care they need

Mothers known to be HIV-infected Should be provided with lifelong antiretroviral therapy or antiretroviral prophylaxis interventions to reduce HIV transmission through breastfeeding according to WHO recommendations.

Recommendation 2

Which breastfeeding practices and for how long

Mothers known to be HIV-infected (and whose infants are HIV-uninfected or of unknown HIV status) Should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided.

Recommendation 3

When mothers decide to stop breastfeeding

Mothers known to be HIV-infected Who decide to stop breastfeeding at any time should stop gradually within 1 month. Mothers or infants who have been receiving ARV prophylaxis should continue prophylaxis for 1 week after breastfeeding is fully stopped. Stopping breastfeeding abruptly is not advisable.

Recommendation 4

What to feed infants when mothers stop breastfeeding

When *mothers known to be HIV-infected* Decide to stop breastfeeding at any time, infants should be provided with safe and adequate replacement feeds to enable normal growth and development. Alternatives to breastfeeding include:

- For infants less than 6 months of age:
  - Commercial infant formula milk as long as home conditions outlined in Recommendation #5 below are fulfilled,
  - Expressed, heat-treated breast milk (see Recommendation #6 below),

  Home-modified animal milk is not recommended as a replacement food in the first 6 months of life.
- For children over 6 months of age:
  - Commercial infant formula milk as long as home conditions outlined in Recommendation #5 are fulfilled,
  - When animal milk is given, it should be boiled for infants under 12 months unless pasteurised, and be given in addition to other food providing an adequate macro- and micronutrient intake.

  All children need complementary foods from 6 months of age.

(continued)

Box 14.1 (continued)

Recommendation 5

Conditions needed to safely formula feed

Mothers known to be HIV-infected should only give commercial infant formula milk as a replacement feed to their HIV-uninfected infants or infants who are of unknown HIV status, when all the following conditions are met:

a. Safe water and sanitation are assured in the household and the community
b. The mother or other caregiver can reliably provide sufficient infant formula milk to support normal growth and development of the infant
c. The mother or caregiver can prepare it cleanly and frequently enough so that it is safe and carries a low risk of diarrhoea and malnutrition
d. The mother or caregiver can give infant formula milk exclusively in the first 6 months
e. The family is supportive of this practice
f. The mother or caregiver can access health care that offers comprehensive child health services

These descriptions are intended to give simpler and more explicit meaning to the concepts represented by AFASS (acceptable, feasible, affordable, sustainable, and safe).

Recommendation 6

Heat-treated, expressed breast milk

Mothers known to be HIV-infected may consider expressing and heat-treating breast milk as *an interim feeding strategy*:

- In special circumstances such as when the infant is born with low birth weight or is otherwise ill in the neonatal period and unable to breastfeed;
- When the mother is unwell and temporarily unable to breastfeed or has a temporary breast health problem such as mastitis;
- To assist mothers to stop breastfeeding; or
- If antiretroviral drugs are temporarily not available.

Recommendation 7

When the infant is HIV-infected

If infants and young children are known to be HIV-infected, mothers are strongly encouraged to exclusively breastfeed for the first 6 months of life and continue breastfeeding as per the recommendations for the general population, up to 2 years or beyond.

to encourage early abrupt weaning at 4 months or continued breastfeeding for as long as the women chose. There was no significant difference between the groups in the rate of HIV-free survival at 2 years among the children even in the absence of antiretroviral prophylactic drugs (68% in the intervention arm with early weaning and 64% in the control arm). In addition, the children who were infected with HIV by 4 months had a higher mortality by 24 months if breastfeeding was stopped early (74 vs. 55%). These results led WHO to change their recommendations (see Box 14.1) from supporting early weaning at 6 months to continued breastfeeding until a nutritionally adequate and safe diet without breast milk can be provided [27].

Complementary feeding from 6 months onwards is needed as human milk is inadequate to satisfy the infant's nutritional needs. A good and balanced diet consists of adequate and culturally acceptable

macro- and micronutrients [28]. Numerous studies have been done identifying micronutrient deficiencies in young infants with good evidence for single-micronutrient supplement benefits—particularly for vitamin A and zinc [19, 22, 29, 30].

High quality and adequate complementary feeding is a necessity to avoid undernutrition including stunting (very low height according to age [length/height-for-age < − 2 z-scores]) and wasting (weight-for-length/height <−2 z-scores below the mean). Undernutrition is in many settings widespread at an early age, particularly in Sub-Saharan Africa and South-East Asia, with up to half of the children stunted at 2 years [19, 21, 22, 31]. Undernutrition has severe consequences in the short term with increased vulnerability to morbidity and mortality, and also in the long term with less fortunate prospects in adult life [19, 22, 32–34], and adds to the morbidity from exposure to HIV even when uninfected and the added risk of growing up without parents [3].

Multiple factors seem to be involved in the causal web leading to stunting including environmental and agricultural, economic, political, contextual factors, and in particular poverty, food security, health, and care [19]. Studies have shown that undernutrition is strongly related with wealth—with most undernutrition in the poorest part of the population [31, 35, 36].

Good community programmes promoting adequate complementary feeding are highly diet and context specific, and drawing conclusions on which public health efforts are most efficacious has been difficult. A review from 2008 indicated that food support in food insecure situations is beneficial in terms of improving child growth [22, 86].

Formula Feeding

While exclusive replacement feeding (complete avoidance of breastfeeding) nearly eliminates the risk of postnatal HIV transmission from HIV-positive women to their infants, in many low- and middle-income countries replacement feeding is not considered to be acceptable, affordable, feasible, sustainable, and safe.

Over the past several years, evidence has been accumulating from Africa on the increased mortality associated with formula feeding in various research studies focusing on prevention of mother-to-child transmission of HIV (PMTCT) [10]. A pooled-meta analysis of studies in low-income countries with low HIV prevalence found that infants who are not breastfed and receive formula milk or other replacement feeding have a 6-fold increased risk of dying in the first 2 months of life, a 4-fold increase between 2 and 3 months, and a 2.5-fold increase between 4 and 5 months compared with those who are breastfed [37].

A trial in Botswana compared the efficacy of exclusive breastfeeding combined with antiretroviral drugs (zidovudine) given to the infant for 6 months vs. formula feeding combined with 1 month of antiretroviral prophylaxis to the infant [38]. The HIV transmission rates at 7 months were 5.6% in the formula-fed infants and 9.0% in the breastfed infants, while the number of infant deaths by month 7 was higher in the formula-fed group than in the breastfed infants (9.3 vs. 4.9%). Findings from Kenya have suggested high mortality and transmission rates among both breastfed and formula-fed children; however, in that study the HIV-free survival was slightly in favour of formula feeding in the study context before the use of antiretroviral prophylaxis during breastfeeding [39, 40].

Evidence of the dangers of formula feeding in non-research settings have also been documented in Botswana. Between November 2005 and February 2006, there were unusually heavy rains and flooding which led to an increase in the incidence of diarrhoea. Not breastfeeding was strongly associated with diarrhoea and death, and most of the deaths were among HIV-exposed infants whose mothers were receiving free formula milk through the PMTCT programme [41]. Recent evidence from Malawi has also found that not being breastfed was significantly associated with declines in nutritional status as evidenced by decreased mean length-for-age, weight-for-age and weight-for-length z-scores [42].

In South Africa, research from routine PMTCT sites has found that an inappropriate choice to formula feed (without WHO AFASS conditions being met) carries a greater risk of HIV transmission

or death than breastfeeding [43]. In another study from the predominantly rural district of Hlabisa in Kwa-Zulu Natal, South Africa, mortality at 3 months in exclusively breastfed infants was 6 vs. 15% in infants given replacement feeds, despite the fact that the women opting not to breastfeed were of higher socioeconomic status [8]. By 18 months of age, the probability of survival was not significantly different for HIV-uninfected infants, whether they were breastfed or formula-fed from birth, despite these mothers and infants receiving substantial support to make and practice appropriate infant feeding choices [44]. Therefore, as in the MASHI study, the avoidance of breastfeeding gave no survival gain for these infants. Programs supporting formula feeding are also associated with substantial costs, either to the families and/or to the health systems [27], and can have several related drawbacks [45].

A small study in South Africa that assessed contamination of milk bottles at clinics and in the homes found high levels of contamination with faecal bacteria (67% of clinic samples and 81% of home samples). The study also found evidence of poor formula preparation with over-dilution occurring among 28% of clinic samples and 47% of home samples [46].

Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV

Due to high child mortality observed in many resource-limited settings in the absence of breastfeeding, strategies to reduce HIV transmission while breastfeeding were sought. As it was known that antiretroviral drugs reduce HIV viral load, several studies investigated the degree to which different regimens of antiretroviral prophylaxis given to the mother, the infant, or both could reduce transmission of HIV from mother-to-child. Uncertainty regarding actual prophylactic effects had to be balanced against concerns regarding safety, resistance, and implementation issues. Initially, single dose or short course regimens around the time of the delivery with maternal antiretroviral prophylaxis (zidovudine or nevirapine) was used. It was later found that a longer duration of prophylaxis that provided maternal cover during pregnancy, delivery, and the complete duration of breastfeeding was more efficacious than shorter regimens. A cost-effectiveness discussion came up in parallel with new discoveries in favour of longer and more intensive regimens. The table below summarizes various studies on maternal and infant regimens that have been used and their effects [27, 38, 47–60].

Combination regimens for mothers or infants are now preferred as they seem to be more efficacious. The main aim when mothers are treated is to suppress HIV viral load to very low levels. Furthermore, single drug regimens can lead to the development of resistant HIV strains among infants or mothers.

When an HIV-infected pregnant woman receives highly active antiretroviral therapy for her own health, it is also recommended that her infant receives prophylaxis (e.g., nevirapine) from birth up to 6 weeks of age, regardless of the feeding modality (breast milk or not). This double protection among infants whose mothers receive HAART or among infants not breastfeeding for 6 weeks will counterbalance some of the increased risk of HIV transmission during delivery. An aim when mothers are treated is that HIV viral load is suppressed to very low levels.

If an HIV-infected pregnant woman does not need antiretroviral therapy for her own health (e.g., when the mother has no clinical signs of advanced stage HIV and CD4 is above 350×10^6/L), then antiretroviral prophylaxis is needed for the pregnant woman during pregnancy and delivery (e.g., with a triple drug regimen from early in pregnancy to 1 week after delivery or with zidovudine during pregnancy up to 1 week after delivery, single dose nevirapine and lamivudine during delivery, and lamivudine for 1 week post-delivery), and for her breastfeeding infant from delivery throughout the breastfeeding period (e.g., with nevirapine and/or lamivudine from birth to 1 week after complete breastfeeding cessation).

With optimal maternal antiretroviral treatment (HAART for maternal health) or maternal/infant prophylaxis during breastfeeding, postnatal HIV transmission from mother-to-child can be reduced dramatically (Table 14.1). Most of the commonly used combinations of antiretroviral treatment are in

Table 14.1 Summary from large trials on the use of antiretroviral prophylaxis to prevent postnatal transmission of HIV

Year (published), name of trial/study and setting	Regimen given to mother	Regimen given to infant	Results and main contribution
2008: SWEN [61]	Control: single dose nevirapine (during labour)	Control: single dose nevirapine	46% decrease in postnatal HIV infection at 6 weeks in infants uninfected at birth in intervention compared with the control arm
Ethiopia, India and Uganda	Intervention: single dose nevirapine (during labour)	Intervention: single dose nevirapine + daily nevirapine until 6 weeks postpartum	Continued risk of postnatal HIV transmission after the regimens were discontinued in infants who continued to be breastfed
2008: PEPI trial [62]	Control: single dose nevirapine	Control: single dose nevirapine + 1 week of zidovudine	At 9 months, HIV-1 infection rate was 10.6% in the control
Malawi	Intervention 1: single dose nevirapine	Intervention 1: single dose nevirapine + 14 weeks daily nevirapine	compared to 5.2% in intervention 1 and 6.4% in intervention 2
	Intervention 2: single dose nevirapine	Intervention 2: single dose nevirapine + 14 weeks daily nevirapine and zidovudine	Continued risk of postnatal HIV transmission after the regimens were discontinued in infants who continued to be breastfed
2008: MITRA study [63]	Zidovudine and lamivudine to mothers from 36 weeks	Zidovudine and lamivudine to infant first 1 week	Cumulative HIV transmission was 3.8% at 6 weeks and 4.9% at 6 months of age
Tanzania	gestation to 1 week postpartum	postpartum followed by daily lamivudine to the infants for a maximum of 6 months	Risk of postnatal infection from 6 weeks to 6 months was 1.1%
2009: Kesho Bora [64]	Control: Zidovudine started in end of pregnancy 28–36 weeks + single dose nevirapine at birth + zidovudine and lamivudine first 1 week postpartum	Control: single dose nevirapine at birth + zidovudine for first 1 week postpartum	Rates of HIV infection at birth similar in both arms (around 2%)
Burkina Faso, Kenya, and South Africa	Intervention: antiretroviral therapy (three drugs) started 28–36 weeks pregnancy till 6 months of breastfeeding	Intervention: single dose nevirapine at birth + zidovudine for first 1 week postpartum	At age 6 months cumulative HIV infection rates were 4.9% in the intervention arm compared to 8.5% control arm
			Between 6 weeks and 6 months, the postnatal infection rate was 1.6% in the intervention compared to 3.7% control arm
2009: Mma Bana [65]	Intervention 1: triple drug HAART regimen with	Intervention 1: single dose nevirapine at birth +	The rates of viral suppression at delivery and during breastfeeding
Botswana	nucleoside/non-nucleoside drugs	zidovudine for first 4 weeks postpartum	were similar between the two HAART regimens
	Intervention 2: triple drug HAART regimen including a protease-inhibitor (started 26–34 weeks through 6 months of breastfeeding)	Intervention 2: single dose nevirapine at birth + zidovudine for first 4 weeks postpartum	The cumulative infant HIV infection rate at age 6 months was 1% and 0.4% in interventions 1 and 2, respectively
2009: MITRA plus [66]	Triple drug HAART regimen (started at 34 weeks and continuing through 6 months of breastfeeding)		Cumulative risk of HIV infection was 5% at 6 months and 6% at 18 months of age
Tanzania			The risk of postnatal infection between 6 weeks and 6 months was only 1%
2009: BAN study [67]	Control: single dose nevirapine at birth + zidovudine	Control: single dose nevirapine at birth + zidovudine	The cumulative probability of HIV infection at age 6 months in
Malawi	and lamivudine first 1 week postpartum	and lamivudine first 1 week postpartum	infants uninfected with HIV at birth was 6.4% in the control
	Intervention: single dose nevirapine at birth + zidovudine and lamivudine first 1 week postpartum + HAART from 1 week till 6 months postpartum	Intervention 2: daily nevirapine to infant from 1 week to 6 months postpartum	arm, 3.0% in the intervention 1 arm, and 1.8% in the intervention 2 arm ($p < 0.001$ vs. control arm)
	Intervention 2: single dose nevirapine at birth + zidovudine and lamivudine first 1 week postpartum		

general well tolerated. The choice of antiretroviral regimen is a balance between efficacy, side effects, cost, and availability—both when given as treatment and when given as prophylaxis.

Feeding of Known HIV-Positive Infants and Children

Children living with HIV have several fold increased morbidity and mortality [2, 44]. The mortality among HIV-infected compared to uninfected children is around 10-fold in the absence of antiretroviral therapy. The risk of malnutrition is also increased [68], partly due to oral infections, malabsorption, diarrhoea, increased metabolic requirements, and cytokine-mediated wasting [2, 69].

Among the children who are malnourished, the risk of death is also several folds higher than among HIV-negative children [70]. The presentation of malnutrition among HIV-infected children has been reported to have a slightly different picture, with more often marasmus and less often pure kwashiorkor compared to among non-infected children [71]. HIV-positive infants also more often suffer from prolonged diarrhoea which can be caused by several pathogens. Cryptosporidium parvum is one of the linking pathogens which is strongly associated with both HIV and malnutrition.

Antiretroviral therapy is both preventive and therapeutic strategy reducing morbidity and mortality among HIV-infected children [2, 72]. With good antiretroviral therapy, the morbidity and mortality reduce substantially [2], but are still far above what is expected among HIV-negative children. In addition, the antiretroviral therapy including drugs such as protease-inhibitors can cause side effects such as lipodistrophy, where the fat distribution in the face and the extremities is reduced, while fat is stored in abdominal areas [69]. In addition to antiretrovirals, cotrimoxazole is also recommended as it reduces the risk of several infections.

The energy requirements among HIV-infected children is higher than those not infected [69], particularly with advanced disease. In absence of antiretroviral therapy, research indicates that there is a need for micronutrient supplementation as many HIV-infected children have micronutrient deficiencies [73]. Several deficiencies have been suggested to be important for those who are HIV-positive including vitamin A, B2, B6, B12, C, E, folic acid, and zinc. It is less clear whether there is a need for micronutrient supplementation to HIV-infected children who are treated well with antiretroviral drugs.

The WHO Guidelines on Infant Feeding with a Brief Historical Background

In order to guide health workers in assisting women to make appropriate infant feeding choices, WHO and United Nations Children's Fund (UNICEF) developed the Global Strategy for Infant and Young Child Feeding [14]. The recommendation for women known to be HIV-positive was initially avoidance of all breastfeeding where replacement feeding was acceptable, feasible, affordable, sustainable, and safe (AFASS[1]). Otherwise, exclusive breastfeeding for the first months of life was recommended followed by early breastfeeding cessation as soon as feasible, when conditions for safe replacement feeding could be met. This guideline was revised in 2007 following the results from the Zambian breastfeeding study [74], and stated that "at six months, if replacement feeding is still not acceptable,

[1] The AFASS criteria are meant to guide health workers in assisting women to make infant feeding choices that are appropriate to their individual circumstances. The translation of this recommendation into operational settings is a challenge for health workers and counsellors as there is little guidance on what the terms "acceptable," "sustainable," "safe," and "feasible" mean in practice.

feasible, affordable, sustainable and safe, continuation of breastfeeding with additional complementary foods is recommended."

Between 2007 and 2009, several large trials were underway in South Africa, Zambia, Zimbabwe, and Botswana to assess different feeding strategies for HIV-positive women including exclusive breastfeeding and early cessation of breastfeeding as well as ARV prophylaxis regimens for breastfeeding infants and mothers. Following a review of these trial results, WHO released revised guidelines and recommendations in 2010 (see Box 14.1). In these guidelines, there is greater emphasis placed on ensuring the optimal health of the mother. The first recommendation supports that mothers receive the care that they need through antiretroviral treatment or prophylaxis in line with the 2010 WHO recommendations on antiretroviral drugs for pregnant women and infants [75]. Furthermore, there is a recommendation that either the infant or the mother receive antiretroviral prophylaxis for the duration of breastfeeding to reduce postnatal transmission. With regard to infant feeding mode, the guidelines recommend exclusive breastfeeding for HIV-positive women for 6 months with continued breastfeeding with complimentary feeding until 12 months. In contrast to previous guidelines, early and abrupt cessation is no longer recommended. The new guideline sets out six clear requirements for safe formula feeding including reliability of supplies. This is particularly relevant for countries such as South Africa and Botswana where the governments provide free formula milk to HIV-positive women choosing not to breastfeed.

These revised recommendations provide an opportunity for policy makers and health workers to utilize the accumulated evidence to initiate a period of rapid reductions in postnatal HIV transmission through access to antiretrovirals and optimal infant feeding.

Strategies to increase child survival in Low- and high-income countries

In high-income countries, treatment and prevention guidelines and choices regarding infant feeding in the context of maternal HIV infection are less complicated. Most HIV-positive women in these settings practice replacement feeding. In low-income countries, infant feeding policies are guided by the local context. In most contexts in sub-Saharan Africa, it is clear that avoidance of breastfeeding causes more harm for infants even among HIV-positive women. In some settings such as South Africa and Botswana, the governments have chosen to provide HIV-positive women with an alternative to breastfeeding by providing free formula milk. However, research has found that even with the provision of free milk, the risks of replacement feeding can outweigh the risks of breastfeeding in terms of child survival [38, 43, 76].

The recent WHO guidelines on HIV and infant feeding which are being adopted by many low-income countries [27] have led to increased access to antiretroviral drugs for mothers and infants. This has been shown to markedly decrease breastfeeding HIV transmission and made replacement feeding less beneficial with regard to HIV-free survival. The challenge of HIV and breastfeeding and the research conducted over the past decade now open up an opportunity to use this knowledge to revitalize support for exclusive breastfeeding.

HIV-Related Challenges with Infant Feeding

The challenge of improving infant feeding practices for HIV-positive women needs to be understood within a context of infant feeding in the general population. In most of the world including much of sub-Saharan Africa, around 95% of mothers initiate breastfeeding after birth, and most of them continue to breastfeed for more than a year [77]. However, in many settings, mixed feeding during the

first months of life (when both breast milk and non-human milk or other solid or semisolid food given to the infant) is the cultural norm [78–81]. It is against this background that infant feeding recommendations for women with HIV are being implemented. If women with HIV are to succeed in practicing exclusive infant feeding (i.e., only breastfeeding or only formula feeding during the first months of life), then changes in the infant feeding practices in the general population are necessary to ensure that exclusive breastfeeding is a norm rather than an exception, and that women opting for exclusive breast- or formula feeding are not stigmatized.

Mothers with HIV often face social and practical concerns that influence the infant feeding choice. The most immediate concerns relate to stigma and disclosure of HIV status [82, 83]. In cultures where breastfeeding is the norm, as is the case in most low-income settings, not breastfeeding can stigmatize the mother as it is outside the local norm. In some cases, it may even be an indication to the community that the mother is HIV-positive. This threatens the mother's confidentiality about her status and can in some cases lead to rejection by the partner or family, or even violence. To avoid this, some mothers will adapt to the culturally accepted practices and breastfeed in public, while using formula milk in private [26].

Another issue is that mothers in some cases are not the decision makers for issues concerning the feeding of their own infants [82, 83]. Depending on the community, such decisions may rest with e.g. the partner, the mother-in-law, or the woman's own mother. Therefore, the mother may be faced with challenging the authority of the family structure to implement her desired feeding option. This will be difficult for many women to do. Some mothers make informed choices when counselled in health services, but are pressured to reverse this choice upon returning home, often leading to mixed feeding. When feeding choices are supported by the family, exclusive feeding has been more successful [84].

In addition to social stigma issues, there are also practical constraints and socioeconomic conditions that influence feeding choice [82, 84]. The mother may choose formula feeding and find this option to be impractical and difficult, for example, when preparing infant formula during the night with no electricity, running water, or refrigeration. Finding this too difficult, she might breastfeed at night and use substitutes during daytime.

Another consideration is knowledge on advantages and disadvantages of the various infant feeding options. Health counselling is essential in this respect [84]. However, there are several reports of health counselling where HIV transmission has been overestimated and counselling of simplistic messages which might leave the mothers confused [26, 85].

Health care services and community structures must provide counselling and support for infant feeding that extends beyond the antenatal period. It is important to enable mothers to cope with new challenges and pressures at critical times during the early postpartum period so they make good infant feeding choices within their own personal circumstances.

Summary

Appropriate infant feeding choices are essential for the health of all children. This is just as true for the children of HIV-positive mothers, who have some additional important issues. This includes use of antiretroviral drugs as prophylaxis or therapy to reduce HIV transmission, questions related to duration of different feeding modalities, and questions related to feasibility and acceptability of the choices related to infant feeding and therapy. However, the current guidelines from the WHO on infant feeding in the context of HIV are in most aspects more similar to the recommendations for the general population than they were earlier with more emphasis on the importance of antiretroviral drugs, providing an opportunity for countries to accelerate support for breastfeeding to improve health of all children.

References

1. Ziegler JB, Cooper DA, Johnson RO, Gold J. Postnatal transmission of AIDS-associated retrovirus from mother to infant. Lancet. 1985;1(8434):896–8.
2. Prendergast A, Tudor-Williams G, Jeena P, Burchett S, Goulder P. International perspectives, progress, and future challenges of paediatric HIV infection. Lancet. 2007;370(9581):68–80.
3. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet. 2004;364(9441):1236–43.
4. Chopra M, Doherty T, Goga A, Jackson D, Persson LA. Survival of infants in the context of prevention of mother to child HIV transmission in South Africa. Acta Paediatr. 2010;99(5):694–8.
5. Lehman DA, Farquhar C. Biological mechanisms of vertical human immunodeficiency virus (HIV-1) transmission. Rev Med Virol. 2007;17(6):381–403.
6. Bahl R, Frost C, Kirkwood BR, Edmond K, Martines J, Bhandari N, et al. Infant feeding patterns and risks of death and hospitalization in the first half of infancy: multicentre cohort study. Bull World Health Organ. 2005;83(6):418–26.
7. Kuhn L, Stein Z, Susser M. Preventing mother-to-child HIV transmission in the new millennium: the challenge of breast feeding. Paediatr Perinat Epidemiol. 2004;18(1):10–6.
8. Coovadia HM, Rollins NC, Bland RM, Little K, Coutsoudis A, Bennish ML, et al. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. Lancet. 2007;369(9567):1107–16.
9. Coutsoudis A, Pillay K, Spooner E, Kuhn L, Coovadia HM. Influence of infant-feeding patterns on early mother-to-child transmission of HIV-1 in Durban, South Africa: a prospective cohort study. South African Vitamin A Study Group. Lancet. 1999;354(9177):471–6.
10. Kagaayi J, Gray RH, Brahmbhatt H, Kigozi G, Nalugoda F, Wabwire-Mangen F, et al. Survival of infants born to HIV-positive mothers, by feeding modality, in Rakai, Uganda. PLoS One. 2008;3(12):e3877.
11. Iliff PJ, Piwoz EG, Tavengwa NV, Zunguza CD, Marinda ET, Nathoo KJ, et al. Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. AIDS. 2005;19(7):699–708.
12. Kuhn L, Sinkala M, Kankasa C, Semrau K, Kasonde P, Scott N, et al. High uptake of exclusive breastfeeding and reduced early post-natal HIV transmission. PLoS One. 2007;2(12):e1363.
13. Becquet R, Ekouevi DK, Menan H, Amani-Bosse C, Bequet L, Viho I, et al. Early mixed feeding and breastfeeding beyond 6 months increase the risk of postnatal HIV transmission: ANRS 1201/1202 Ditrame Plus, Abidjan, Cote d'Ivoire. Prev Med. 2008;47(1):27–33.
14. WHO. Global strategy for infant and young child feeding. Geneva: World Health Organisation; 2003.
15. Kuhn L, Aldrovandi GM, Sinkala M, Kankasa C, Semrau K, Mwiya M, et al. Effects of early, abrupt weaning on HIV-free survival of children in Zambia. N Engl J Med. 2008;359(2):130–41.
16. Johnson W, Alons C, Fidalgo L, Piwoz E, Kahn S, Macombe A, et al.: The challenge of providing adequate infant nutrition following early breastfeeding cessation by HIV-positive, food insecure Mozambican mothers. In International AIDS conference. volume WEAD0105. Toronto; 2006.
17. Lunney KM, Jenkins AL, Tavengwa NV, Majo F, Chidhanguro D, Iliff P, et al. HIV-positive poor women may stop breast-feeding early to protect their infants from HIV infection although available replacement diets are grossly inadequate. J Nutr. 2008;138(2):351–7.
18. Piwoz EG, Huffman SL, Quinn VJ. Promotion and advocacy for improved complementary feeding: can we apply the lessons learned from breastfeeding? Food Nutr Bull. 2003;24(1):29–44.
19. Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, et al. Maternal and child undernutrition: global and regional exposures and health consequences. Lancet. 2008;371(9608):243–60.
20. Arpadi S, Fawzy A, Aldrovandi GM, Kankasa C, Sinkala M, Mwiya M, et al. Growth faltering due to breastfeeding cessation in uninfected children born to HIV-infected mothers in Zambia. Am J Clin Nutr. 2009;90(2):344–53.
21. Becquet R, Leroy V, Ekouevi DK, Viho I, Castetbon K, Fassinou P, et al. Complementary feeding adequacy in relation to nutritional status among early weaned breastfed children who are born to HIV-infected mothers: ANRS 1201/1202 Ditrame Plus, Abidjan, Cote d'Ivoire. Pediatrics. 2006;117(4):e701–10.
22. Bhutta ZA, Ahmed T, Black RE, Cousens S, Dewey K, Giugliani E, et al. What works? Interventions for maternal and child undernutrition and survival. Lancet. 2008;371(9610):417–40.
23. Dewey KG, Adu-Afarwuah S. Web appendix 3: systematic review of the efficacy and effectiveness of complementary feeding interventions in developing countries (from: What works? Interventions for maternal and child undernutrition and survival). Lancet. 2008;371(9610):417–40.
24. WHO: Infant and young child feeding: model chapter for textbookds for medical students and allied health professionals. 2009.
25. Coovadia H, Jewkes R, Barron P, Sanders D, McIntyre D. The health and health system of South Africa: historical roots of current public health challenges. Lancet. 2009;374(9692):817–34.

26. Fadnes LT, Engebretsen IM, Moland KM, Nankunda J, Tumwine JK, Tylleskar T. Infant feeding counselling in Uganda in a changing environment with focus on the general population and HIV-positive mothers—a mixed method approach. BMC Health Serv Res. 2010;10(1):260.
27. World Health Organization (WHO), UNICEF, UNFPA, UNAIDS: Guidelines on HIV and Infant Feeding 2010: Principles and recommendations for infant feeding in the context of HIV and a summary of evidence. 2010.
28. World Health Organization (WHO): Global Strategy for Infant and Young Child Feeding. In http://wwwwhoint/nut/documents. Geneva; 2003. [Accessed August, 2011]
29. Chhagan MK, Van den Broeck J, Luabeya KK, Mpontshane N, Tomkins A, Bennish ML. Effect on longitudinal growth and anemia of zinc or multiple micronutrients added to vitamin A: a randomized controlled trial in children aged 6–24 months. BMC Public Health. 2010;10:145.
30. Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. Cochrane Database Syst Rev. 2008;(3):CD005436.
31. Engebretsen IMS, Tylleskär T, Wamani H, Karamagi C, Tumwine JK. Determinants of infant growth in Eastern Uganda: a community-based cross-sectional study. BMC Public Health. 2008;8:418.
32. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? Lancet. 2003; 361(9376):2226–34.
33. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, et al. Maternal and child undernutrition: consequences for adult health and human capital. Lancet. 2008;371(9609):340–57.
34. Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. Lancet. 1993;341(8850):938–41.
35. Chopra M. Risk factors for undernutrition of young children in a rural area of South Africa. Public Health Nutr. 2003;6(7):645–52.
36. Wamani H, Astrom AN, Peterson S, Tumwine JK, Tylleskar T. Predictors of poor anthropometric status among children under 2 years of age in rural Uganda. Public Health Nutr. 2006;9(3):320–6.
37. WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. Lancet. 2000;355(9202):451–5.
38. Thior I, Lockman S, Smeaton LM, Shapiro RL, Wester C, Heymann SJ, et al. Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study. JAMA. 2006;296(7):794–805.
39. Nduati R, John G, Mbori-Ngacha D, Richardson B, Overbaugh J, Mwatha A, et al. Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial. JAMA. 2000;283(9):1167–74.
40. Mbori-Ngacha D, Nduati R, John G, Reilly M, Richardson B, Mwatha A, et al. Morbidity and mortality in breastfed and formula-fed infants of HIV-1-infected women: a randomized clinical trial. JAMA. 2001;286(19):2413–20.
41. Creek TL, Kim A, Lu L, Bowen A, Masunge J, Arvelo W, et al. Hospitalization and mortality among primarily nonbreastfed children during a large outbreak of diarrhea and malnutrition in Botswana, 2006. J Acquir Immune Defic Syndr. 2010;53(1):14–9.
42. Taha T, Nour S, Li Q, Kumwenda N, Kafulafula G, Nkhoma C, et al. The effect of human immunodeficiency virus and breastfeeding on the nutritional status of African children. Pediatr Infect Dis J. 2010;29(6):514–8.
43. Doherty T, Chopra M, Jackson D, Goga A, Colvin M, Persson LA. Effectiveness of the WHO/UNICEF guidelines on infant feeding for HIV-positive women: results from a prospective cohort study in South Africa. AIDS. 2007;21(13):1791–7.
44. Rollins NC, Becquet R, Bland RM, Coutsoudis A, Coovadia HM, Newell M-L. Infant feeding, HIV transmission and mortality at 18 months: the need for appropriate choices by mothers and prioritization within programmes. AIDS (London, England). 2008;22(17):2349–57.
45. Doherty T, Sanders D, Goga A, Jackson D. Implications of the new WHO guidelines on HIV and infant feeding for child survival in South Africa. Bull World Health Organ. 2011;89(1):62–7.
46. Andresen E, Rollins NC, Sturm AW, Conana N, Greiner T. Bacterial contamination and over-dilution of commercial infant formula prepared by HIV-infected mothers in a Prevention of Mother-to-Child Transmission (PMTCT) Programme, South Africa. J Trop Pediatr. 2007;53(6):409–14.
47. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med. 1994;331(18):1173–80.
48. Kilewo C, Karlsson K, Massawe A, Lyamuya E, Swai A, Mhalu F, et al. Prevention of mother-to-child transmission of hiv-1 through breast-feeding by treating infants prophylactically with Lamivudine in Dar es Salaam, Tanzania: the mitra study. J Acquir Immune Defic Syndr. 2008 Jul 1;48(3):315–23.
49. Kilewo C, Karlsson K, Ngarina M, Massawe A, Lyamuya E, Swai A, et al. Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers with triple antiretroviral therapy in Dar es Salaam, Tanzania: the Mitra Plus study. J Acquir Immune Defic Syndr. 2009;52(3):406–16.
50. World Health Organisation: Rapid advice: infant feeding in the context of HIV. 2009.

51. World Health Organisation: Rapid advice: use of antiretroviral drugs for treating pregnant women and preventing HIV Infection in infants. 2009.
52. Human Sciences Research Council: South African National HIV prevalence, behavioural risks and mass media household survey. 2002.
53. Chasela CS, Hudgens MG, Jamieson DJ, Kayira D, Hosseinipour MC, Kourtis AP, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. N Engl J Med. 2010;362(24):2271–81.
54. Kumwenda NI, Hoover DR, Mofenson LM, Thigpen MC, Kafulafula G, Li Q, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. N Engl J Med. 2008;359(2):119–29.
55. Shapiro RL, Hughes MD, Ogwu A, Kitch D, Lockman S, Moffat C, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. N Engl J Med. 2010;362(24):2282–94.
56. Bedri A, Gudetta B, Isehak A, Kumbi S, Lulseged S, Mengistu Y, et al. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. Lancet. 2008;372(9635):300–13.
57. The Kesho Bora Study Group. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. Lancet Infect Dis. 2011;11(3):171–80. Epub 2011 Jan 13.
58. Volmink J, Siegfried NL, van der Merwe L, Brocklehurst P. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. Cochrane Database Syst Rev. 2007;(1):CD003510.
59. World Health Organisation: Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents. 2009.
60. Saba J, Haverkamp G, Gray G, et al. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. Lancet. 2002;359(9313):1178–86.
61. Six week extended dose nevirapine (SWEN) Study team. Extended dose nevirapine at 6 weeks of age for infants to prevent HIV transmission via breatsfeeding in Ethiopia, India and Uganda: an analysis of 3 randomised controlled trials. Lancet. 2008;372:300–13.
62. Kumwenda N, Hoover D, Mofenson L. Extended antiretroviral prophylaxis to reduce breastmilk HIV-1 transmission. N Engl J Med. 2008;359:119–29.
63. Kilewo C, Karlsson K, Massawe A, Mitra Study Team. Prevention of Mother-to-Child Transmission of HIV-1 through breastfeeding by treating infants prophylactically with lamivudine in Dar es Salaam. J Acquir Immune Defic Syndr. 2008;48:315–23.
64. de Vincenzi I, Kesho Bora Study Group: Triple antiretroviral prophylaxis during pregnancy and breastfeeding compared with short-ARV prophylaxis to prevent mother-to-child transmission of HIV-1: the Kesho-Bora randomised controlled trials in 5 sites in Burkina Faso, Kenya and South Africa (LBPE C01). In 5th International AIDS Society conference on HIV pathogenesis, treatment and prevention. Cape Town, South Africa; 2009.
65. Shapiro R, Hughes M, Ogwu A, et.al.: The Mma Bana Study: randomised trial comparing highly active antiretroviral therapy regimens for virologic efficacy and the prevention of mother-to-chid transmission of HIV transmission amongst breastfeeding women in Botswana (WeLB B101). In 5th International AIDS Society conference on hiv pathogenesis, treatment and prevention Cape Town, South Africa; 2009.
66. Kilewo C, Karlsson K, Ngarina M: Prevention of mother-to child transmission of HIV-1 through breastfeeding by treating mothers with triple antiretroviral therapy in Dar es Salaam, Tanzania. The MITRS-Plus study. J Acquir Immune Defic Syndr 2009, on line printing at www.jaids.com. October 2009. [Accessed August, 2011]
67. Chasela C, Hudgens M, Jamieson D, et.al.: Both maternal HAART and daily infant nevirapine (NVP) are effective in reducing HIV-1 transmission during breastfeeding in a randomised trial in Malawi: 28 week results of the Breastfeeding, Antiretroviral and Nutrition (BAN) study (WeLB C103). In 5th International AIDS society conference on hiv pathogenesis, treatment and prevention. Cape Town, South Africa; 2009.
68. Ramalho LC, Goncalves EM, de Carvalho WR, Guerra-Junior G, Centeville M, Aoki FH, et al. Abnormalities in body composition and nutritional status in HIV-infected children and adolescents on antiretroviral therapy. Int J STD AIDS. 2011;22(8):453–6.
69. Miller TL. Nutrition in paediatric human immunodeficiency virus infection. Proc Nutr Soc. 2000;59(1):155–62.
70. Fergusson P, Chinkhumba J, Grijalva-Eternod C, Banda T, Mkangama C, Tomkins A. Nutritional recovery in HIV-infected and HIV-uninfected children with severe acute malnutrition. Arch Dis Child. 2009;94(7):512–6.
71. Amadi B, Kelly P, Mwiya M, Mulwazi E, Sianongo S, Changwe F, et al. Intestinal and systemic infection, HIV, and mortality in Zambian children with persistent diarrhea and malnutrition. J Pediatr Gastroenterol Nutr. 2001;32(5):550–4.
72. Guarino A, Bruzzese E, De Marco G, Buccigrossi V. Management of gastrointestinal disorders in children with HIV infection. Paediatr Drugs. 2004;6(6):347–62.
73. Drain PK, Kupka R, Mugusi F, Fawzi WW. Micronutrients in HIV-positive persons receiving highly active antiretroviral therapy. Am J Clin Nutr. 2007;85(2):333–45.

74. WHO. HIV and infant feeding: new evidence and programmatic experience. Geneva: WHO; 2007.
75. World Health Organisation. Rapid advice: use of antiretroviral drugs for treating pregnant women and preventing HIV Infection in infants. Geneva: WHO; 2009.
76. Creek T, Luo C, Quick T: HIV-exposed children highly affected by deadly outbreak of diarrhea and severe acute malnutrition - Botswana, 2006. In 2006 HIV/AIDS implementers meeting of the President's emergency plan for AIDS relief. Durban; 2006.
77. Lauer JA, Betran AP, Victora CG, De Onis M, Barros AJ. Breastfeeding patterns and exposure to suboptimal breastfeeding among children in developing countries: review and analysis of nationally representative surveys. BMC Med. 2004;2(1):26.
78. Chopra M, Piwoz E, Sengwana J, Schaay N, Dunnett L, Saders D. Effect of a mother-to-child HIV prevention programme on infant feeding and caring practices in South Africa. S Afr Med J. 2002;92(4):298–302.
79. Leshabari SC, Blystad A, de Paoli M, Moland KM. HIV and infant feeding counselling: challenges faced by nurse-counsellors in northern Tanzania. Hum Resour Health. 2007;5:18.
80. Osman H, Elzein L, Wick L. Cultural beliefs that may discourage breastfeeding among Lebanese women: a qualitative analysis. Int Breastfeed J. 2009;4(1):12.
81. Fjeld E, Siziya S, Katepa-Bwalya M, Kankasa C, Moland KM, Tylleskar T. 'No sister, the breast alone is not enough for my baby' A qualitative assessment of potentials and barriers in the promotion of exclusive breastfeeding in southern Zambia. Int Breastfeed J. 2008;3(1):26.
82. Thairu LN, Pelto GH, Rollins NC, Bland RM, Ntshangase N. Sociocultural influences on infant feeding decisions among HIV-infected women in rural Kwa-Zulu Natal, South Africa. Matern Child Nutr. 2005;1(1):2–10.
83. Doherty T, Chopra M, Nkonki L, Jackson D, Greiner T. Effect of the HIV epidemic on infant feeding in South Africa: "When they see me coming with the tins they laugh at me". Bull World Health Organ. 2006;84(2):90–6.
84. Doherty T, Chopra M, Nkonki L, Jackson D, Persson LA. A longitudinal qualitative study of infant-feeding decision making and practices among HIV-positive women in South Africa. J Nutr. 2006;136(9):2421–6.
85. Chopra M, Rollins N. Infant feeding in the time of HIV: rapid assessment of infant feeding policy and programmes in four African countries scaling up prevention of mother to child transmission programmes. Arch Dis Child. 2008;93(4):288–91.
86. Briend A, Van den Broeck J, Fadnes LT. Target weight gain for moderately wasted children during supplementation interventions - a population-based approach. Public Health Nutr. 2011;1–7.

Chapter 15
Undernutrition and Hearing Impairment

Bolajoko O. Olusanya

Key Points

- Hearing is an essential component of the human brain and the central nervous system that facilitates interpersonal communication and interaction.
- This chapter highlights the relationship between undernutrition and human development in early childhood and provides an overview of the auditory system as a basis for exploring the association and possible pathways between undernutrition and hearing impairment in the first year of life.

Keywords Child development • Developmental disability • Hearing loss • Early intervention • Protein-energy deficiency • Micronutrient deficiency

Introduction

From birth, humans develop and acquire functional skills in key interdependent domains of motor (gross and fine); language (receptive and expressive); cognitive; and psychosocial development as a basis for later educational and vocational attainment. While the most essential development generally begins from conception through the first 5 years of life, the first year of life is the fastest period of postnatal growth as well as the period most sensitive to stimulation and nurturing (or the lack of it) for the developing brain [1–4]. The human brain begins to develop in utero with the formation of neural cells followed by a sequence of cell migration and differentiation. As from the fourth month of life peripheral nerve fibers gradually acquire membranous sheath known as myelin to facilitate conduction from the nerve to the target organ and vice versa. Until about school age the brain develops rapidly through the processes of neurogenesis, axonal and dendritic proliferation, synaptogenesis, cell apoptosis, synaptic pruning, myelination, and gliogenesis and attains its maximum growth within the first 2 years of life as shown in Fig. 15.1.

Adequate nutrition ensures that the energy and nutrients required by these sequential ontogenetic events are supplied to facilitate the maturation and functional development of the brain and the central nervous system. Nutritional deficiencies in the prenatal or immediate postnatal period are therefore

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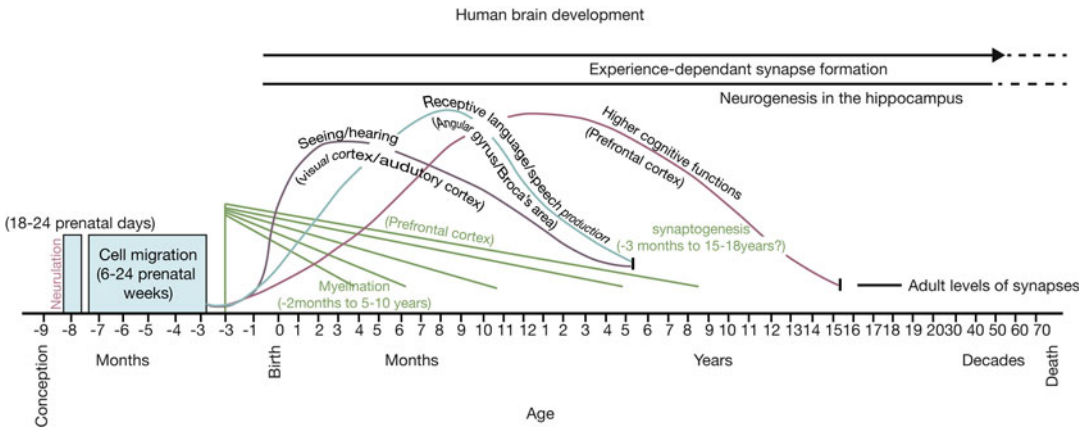

Fig. 15.1 Sequence of human brain development (Grantham-McGregor et al. [1], Reproduced with permission of Elsevier)

likely to disrupt and compromise these ontogenetic processes with long-term effects on the brain's structural and functional capacity [5]. These disruptions usually manifest as developmental delays or deficits across one or more domains.

Nutritional deficiencies can be broadly grouped into deficiencies in protein-energy as evidenced by sub-normal changes in body weight and height; as well as micronutrients comprising essential minerals and vitamins. The impact on brain development varies, depending on the specific nutritional deficiency, its severity and the timing of the deficiency relative to the developmental stage. While functional limitations to optimal early childhood growth and development may also be attributable to genetic factors, infections, exposure to environmental toxins, perinatal and neonatal complications, poverty, trauma, or combinations of these factors, undernutrition is perhaps the most commonly and most convincingly reported risk factor for developmental disabilities globally [6].

Significance of Hearing Impairment in Infancy

Undernutrition is not only a risk factor for a wide spectrum of developmental disabilities such as sensori-motor, cognitive, intellectual and behavioral deficits but also a consequence of developmental disabilities. Of all developmental disorders associated with undernutrition, hearing impairment originating in utero or in early infancy is of special interest because its detection and intervention after the first year of life portend significant adverse consequences which transverse almost all developmental domains. The effects manifest in significant and often life-long deficits in gross and fine motor skills [7], cognitive performance [8], speech and language development [9], and psychosocial development [10]. The pattern of emotional, intellectual, physical, and social development varies within each child and from child to child. However, children with hearing impairment are often faced with greater developmental challenges compared to their hearing peers.

Studies have long demonstrated that a 1 year-old child has a neural mechanism which probably since the sixth month of fetal life has been engaged in a process of separating out those sound patterns which are significant for auditory functioning from the cacophony of the intrauterine and then extrauterine environment [11]. Thus adequate auditory stimulation in infancy is a prerequisite for optimal speech and language development as well as the acquisition of optimal literacy skills. At school age, hearing impairment significantly undermines educational development. This disadvantage continues into adulthood with significant economic and vocational consequences [12, 13], as well as substantial lifetime costs to the society [14, 15].

The timing and duration of sensory maturation within the sequence of the ontogenetic events in brain development also clearly supports the need for priority intervention for hearing impairment in infancy (Fig. 15.1). It is therefore not surprising that early detection and intervention of infants with or at risk of hearing impairment is now routinely mandated in many developed countries while similar initiatives are gradually emerging in developing countries [16].

Overview of the Auditory System and Pathway

The ear develops from three distinctly different parts in the developing embryo: the ectoderm, endoderm, and mesoderm. The definitive auditory structures from the three embryonic germ cell layers are summarized in Table 15.1.

The auditory system is generally considered as an objective and sensitive window into the entire central nervous system and comprises of the peripheral and the central auditory pathways. The peripheral auditory system consists of the external or outer ear, middle ear, and the inner ear (Fig. 15.2).

The central auditory system begins with the cochlea nucleus and traverses the brainstem up to the auditory cortex in the temporal lobe (Fig. 15.3). It consists of the ascending and descending neural fibers with many synaptic stations. The ascending neural pathways from each ear diverge above the

Table 15.1 Auditory structures and the embryonic germ cell precursors

Embryonic germ layers	Definitive auditory structures
Ectoderm from 22 days	Cochlea, spiral ganglion, outer layer of tympanic membrane, cartilaginous portion of external auditory canal and pinna
Endoderm from 28 days	Eustachian tube, lower half of the middle ear and medial layer of tympanic membrane
Mesoderm from 49 days	Ossicles (malleus, incus, and stapes), mastoid process, temporal bone and middle layer of tympanic membrane

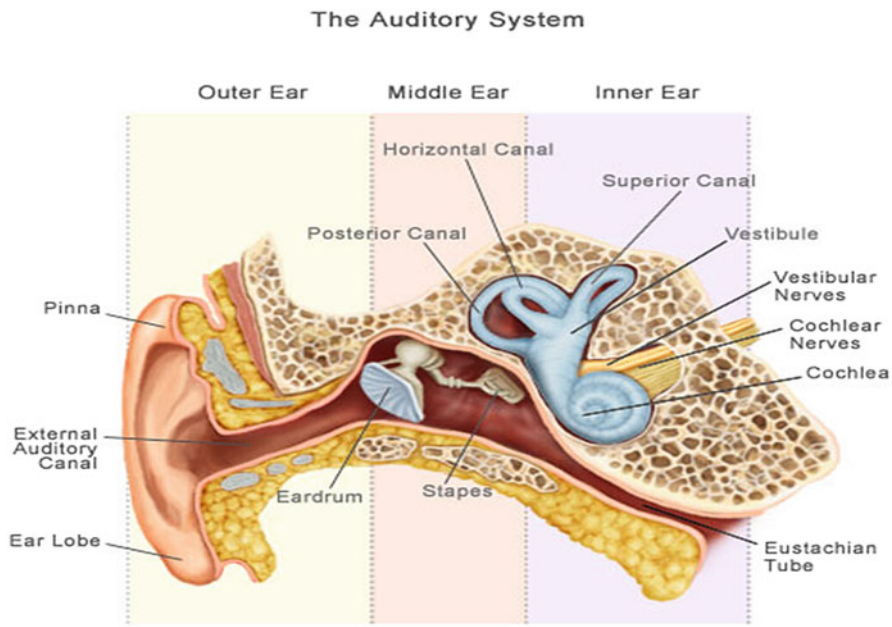

Fig. 15.2 Peripheral auditory system

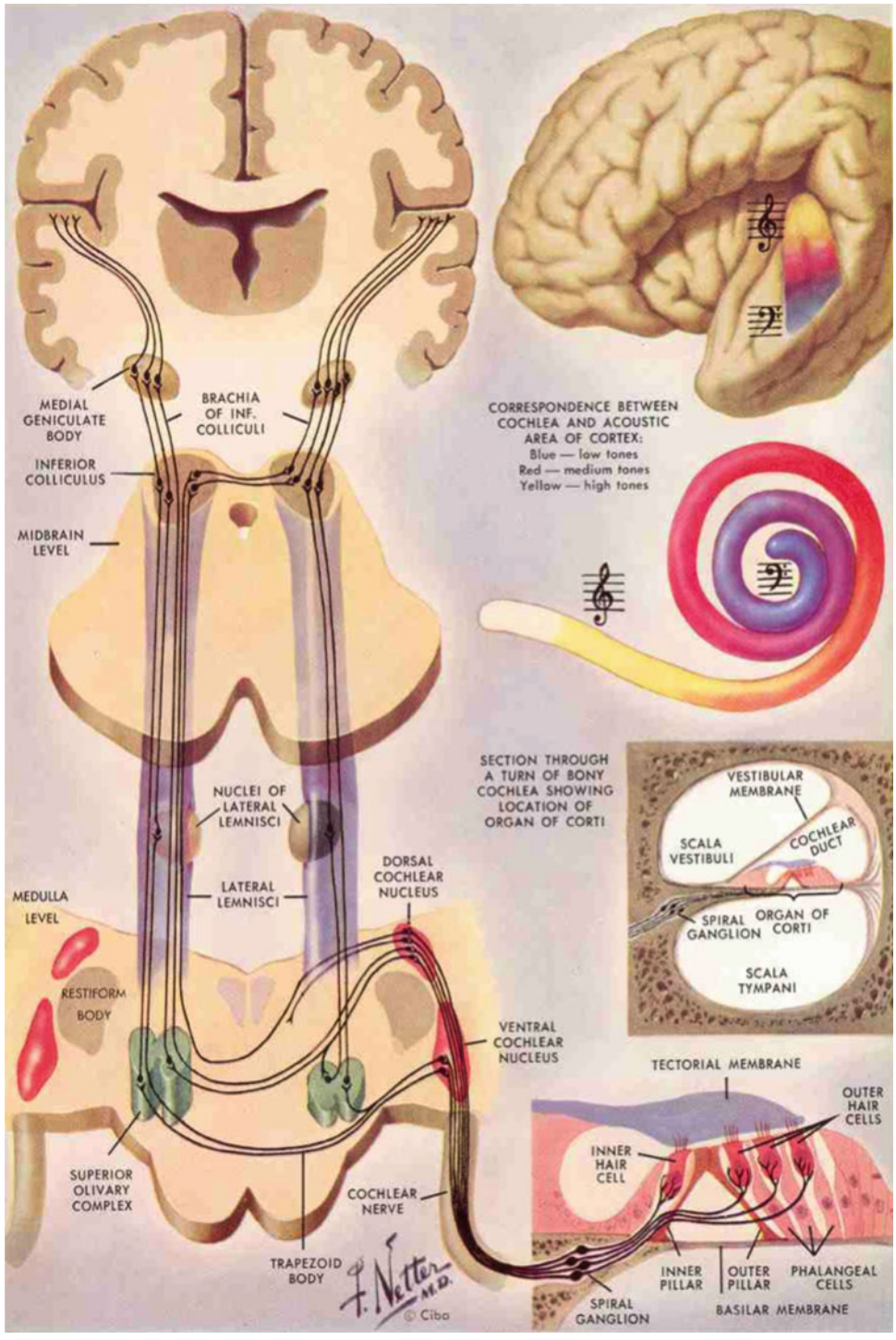

Fig. 15.3 The auditory pathway from the cochlea to the auditory cortex

level of the cochlear nuclei resulting in bilateral representation in both primary auditory cortices. Consequently unilateral lesions above the cochlear nucleus which do not cross the midline do not produce total unilateral hearing loss. The primary auditory cortex is the final relay station for the interpretation of speech signals and together with all the auditory processing centers (the superior olivary complex, the lateral leminisci, the inferior colliculus, medial geniculate body, and the temporal radiations) rostral to the auditory nerve constitutes the central auditory system.

The process of hearing begins with the collection of sounds in the outer ear which are then transmitted through the middle ear ossicles or ossicular chain into the cochlear. Inside the cochlea are highly specialized hair cells which convert the incoming sound energy into electrical signals or impulses for transmission through the eighth nerve to the brain for processing and interpretation. Hearing is impaired if there is any obstruction or malfunctioning anywhere along the entire auditory pathway.

Evaluation of the Auditory Function

Tests of the auditory function can be objective (requiring no active participation of the subject) or subjective (requiring active responses from the subject). However, unlike objective tests which can be conducted from birth, subjective tests can only be conducted reliably as from late infancy (ideally from 9 months of age). The most prominent objective tests of hearing are otoacoustic emissions (OAE) and auditory brainstem response (ABR) while the subjective tests are visual and/or behavioral response audiometry and speech tests. Higher level brainstem and cortical tests for binaural integration and temporal patterning are only just emerging.

OAE is a physiological test for the specific measure of the integrity of the outer hair cells in the cochlea. OAEs, also known as cochlear echoes, are low intensity sounds originating from the active amplification of the outer hair cells and can be elicited in response to clicks or tone bursts presented to the ear. The test will not detect any retro-cochlear dysfunction of the inner hair cells and beyond such as auditory neuropathy spectrum disorder (ANSD). ANSD is a type of hearing impairment in which normal outer ear cell function of the cochlea coexists with abnormal or dys-synchronous ABR. OAE is therefore of limited clinical value in evaluating the full spectrum of the impact of nutritional deficiencies on the auditory system.

In contrast, the ABR is an electro-physiological measure of the function of the auditory pathway from the eighth cranial nerve through the brainstem (Fig. 15.3) and correlates with brain maturation and development. The test is generated from responses to a series of auditory (click/tone) stimuli presented at various intensities. It is therefore a useful indicator of the degree of disruption to the central nervous system resulting from undernutrition. ABR consists of seven waves (I–VII) but waves I–V are more commonly studied (Fig. 15.4). The ABR wave I response is believed to originate from afferent activity of the cranial nerve (CN) VIII fibers (first-order neurons) as they leave the cochlea, wave II is generated by the proximal VIII nerve as it enters the brain stem through the internal auditory canal. ABR wave III arises from second-order neuron activity.

The cochlear nuclei, the trapezoid body, and the superior olivary complex have been suggested as possible sites of origin for wave III. The ABR wave IV, which often shares the same peak with wave V, is thought to arise from pontine third-order neurons mostly located in the superior olivary complex. Wave V is believed to originate from the inferior colliculus in the mid-brain while thalamic (medial geniculate body) origin is suggested for the generation of waves VI and VII. The distal portion of the waveform extends from the cochlea nerve (waves I & II) to the dorsal and ventral cochlear nuclei (wave III). Waves IV and V constitutes the proximal portion of the waveform. The wave V amplitude and inter-peak latency (IPL) I–V (central conduction time) are often significantly correlated with the degree of hearing loss. Maturation of the waveforms occurs in terms of increasing amplitude and

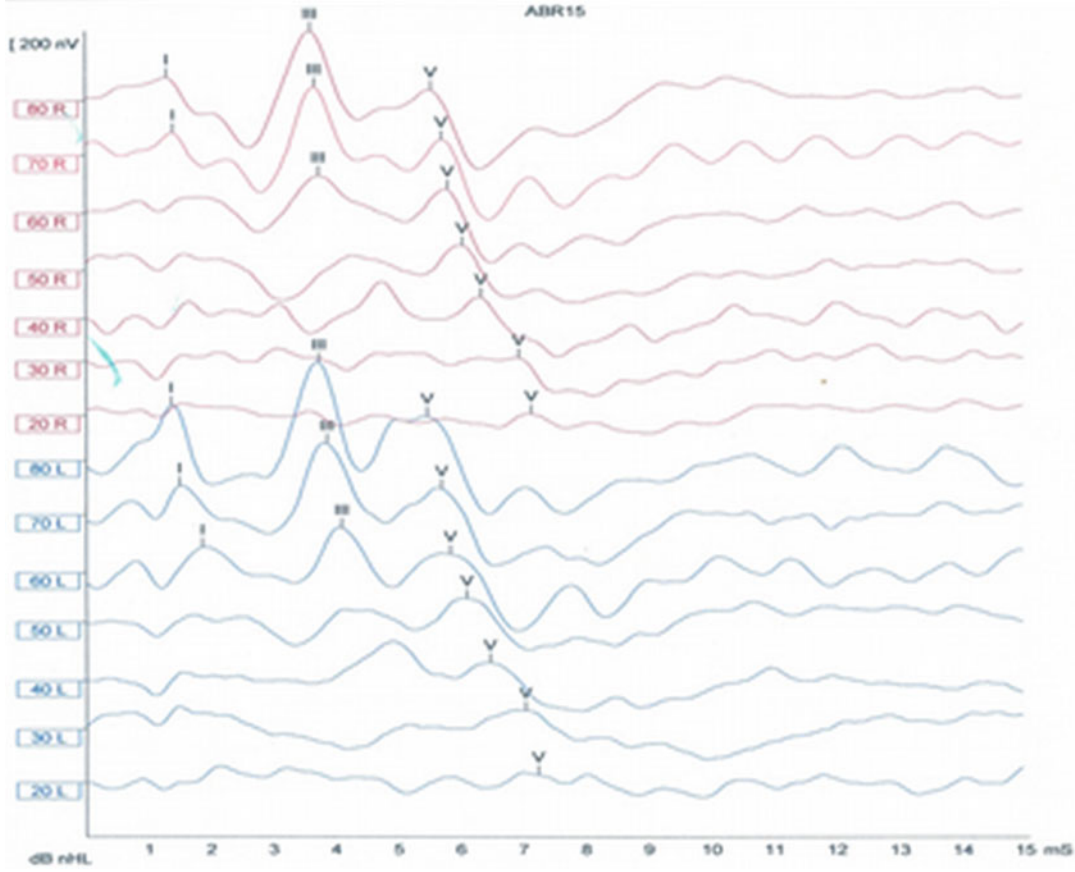

Fig. 15.4 Typical auditory brainstem response waves for left and right ears at stimulus levels 20–80 dBnHL

decreasing duration of IPL I–V in the first year of life to reach the final adult values by the second year. Since wave I has the shortest course it reaches adult values by the age of 2–3 months while wave V with the longest time course may not reach adult values until the second year. Wave III generally occurs midway between waves I and V. Since the ABR in undernourished infants are likely to be abnormal, the abnormalities will more readily reverse or improve with nutritional therapy but may still be significantly different from the ABR of well-nourished infants.

Types and Grades of Hearing Impairment

The term "hearing impairment" is used as a generic term to describe the loss of hearing sensitivity in one or both ears and it is commonly used interchangeably with "hearing loss". Hearing impairment can be classified according to the type of impairment, time of onset and the causality. Hearing impairment affecting the external or middle ear is "conductive" and usually transient because full recovery can be achieved with appropriate treatment. This is commonly as a result of occluding wax in the ear canal, perforations in the tympanic membrane or otitis media with effusion due to infections in the middle ear. However, conductive hearing impairment associated with structural defects or chronic otitis media may be permanent. Hearing impairment is termed "sensorineural" and permanent when

the cochlea or the eighth nerve as far as the auditory cortex in brain is damaged. "Mixed" hearing impairment results from the involvement of both the conductive and sensorineural components in an individual. By etiology, time of onset or pattern, hearing impairment can be classified as congenital, perinatal, or postnatal; hereditary or acquired; sudden, fluctuating or progressive. By degree of severity, hearing impairment can be categorized as slight (16–25 dBHL), mild (26–40 dBHL), moderate (41–55 dBHL), moderately severe (56–70 dBHL), severe (71–90 dBHL), and profound (>90 dBHL) measured by pure-tone averages over octave frequencies 0.5, 1.0, 2.0, and 4.0 kHz [17].

Hearing impairment in early childhood is generally considered as significant when its duration and degree is capable of causing auditory deprivation that would interfere with normal speech and language development. By duration, hearing loss must be persisting or permanent to have a significant impact on speech and language development. This would include sensorineural hearing loss and permanent (rather than transient) conductive hearing loss resulting from recurring otitis media. The World Health Organization (WHO) previously defined "disabling hearing impairment" in children under the age of 15 years as a permanent unaided hearing threshold level in the better ear of 31 dBHL or more [18]. However, this classification excludes children with unilateral hearing loss of any degree as well as those with mild hearing loss. There is ample evidence that children with mild or unilateral permanent hearing loss may experience difficulties with speech, language, educational and psychosocial development [19–21].

The term "hearing impairment" in this chapter refers to unilateral or bilateral sensorineural hearing loss that is mild, moderate, severe or profound, and may or may not be accompanied or preceded by a middle-ear dysfunction consistent with the current international definition of functioning and disabilities in infants and young children [22]. Although middle-ear infections such as otitis media with effusion associated with undernutrition may result in permanent conductive hearing impairment [23], this chapter will not discuss the complex interrelationships between undernutrition, infections, and hearing impairment.

Pathways Between Undernutrition and Hearing Impairment

Possible pathways for the effects of undernutrition on hearing impairment can be conceptualized as shown in Fig. 15.5.

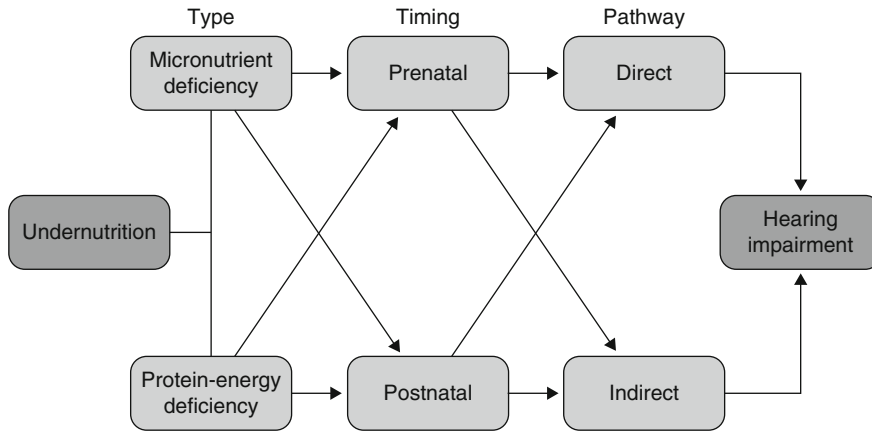

Fig. 15.5 Pathways for hearing impairment associated with undernutrition

The effects of undernutrition can occur prenatally or postnatally and affect the auditory system directly or indirectly. The indirect pathways include infections and inflammation along the auditory system or through adverse pregnancy outcomes such as preterm delivery, low birth weight, and intrauterine growth retardation. However, this chapter will not explore the relationship between these adverse pregnancy outcomes and hearing impairment.

Micronutrient Deficiencies

Micronutrients most commonly associated directly or indirectly with hearing impairment are iodine, iron, zinc, and vitamins A, B_{12}, and D.

Iodine

Iodine is a trace element and a critical component of at least two thyroid hormones (thyroxine or T4, and tri-iodothyronine or T3) vital for human functioning as from 10 to 12 weeks in utero. Fetal thyroid function is dependent on maternal thyroxine for neuronal migration and myelination of the fetal brain. Both maternal and fetal thyroid hormones are therefore involved in the interaction between iodine deficiency and brain development. Iodine deficiency is a common cause of maternal and fetal hypothyroidism frequently accompanied by postnatal hypothyroidism. Iodine-deficiency disorders also include hypertrophy and hyperplasia of the thyroid gland (goiter) due to increased secretion of follicular stimulating hormone in response to low levels of iodine. The most severe form of iodine deficiency in utero causes endemic cretinism characterized by mental retardation, short stature/dwarfism, deaf-mutism (or profound hearing loss) and spasticity. Thus the association between iodine deficiency and neurological deficits including deafness is direct. While the effects of iodine deficiency can be congenital or acquired, the postnatal effects on brain development are not yet fully understood [24, 25].

Hearing impairment is perhaps the most prominent neurological deficit associated with iodine deficiency [26, 27]. The association between iodine deficiency and hearing loss was probably first reported by Bircher in 1883 long before the discovery of ABR in the late 1960s and has since been extensively reported in the literature. The site of the lesion in the auditory pathway could be in the middle ear, cochlea and/or retrocochlea suggesting that iodine deficiency could be associated with conductive, sensorineural or mixed hearing impairment and of various degrees of severity [28, 29]. However, the exact timing of the vulnerability of the auditory system to iodine deficiency and of the events during and after the prenatal period remains unclear [30, 31].

Notwithstanding, several studies in geographical areas with widespread iodine deficiency have shown that the vast majority of persons with neurological endemic cretinism are associated with deaf-mutism or various degrees of hearing loss if untreated. In a multi-ethnic group of 1,222 healthy children (aged 10 months to 4 years) living in France, the risk of high frequency hearing loss was significantly higher among children with mild-to-moderate (10 μg/100 mL) iodine deficiency [32]. In another study from China, iodine content in the hairs of deaf children was found to be much lower than in normal hearing children [33]. Additionally, the hearing thresholds in apparently normal persons residing in iodine-deficient areas have been observed to be higher than hearing thresholds of persons living in areas without iodine deficiency. Hypothyroidism resulting from iodine deficiency or other factors is also well established as a cause of hearing impairment. For example, studies linking hypothyroidism or endemic cretinism in utero with severe hearing impairment or deaf-mutism have observed very low iodine levels in the affected children [26]. Similarly, the long-term effects of

hearing impairment in children with hypothyroidism in functional domains of language and auditory processing skills have also been documented [28]. In one of the rare studies linking undernutrition with ANSD François et al. reported the presence of OAE but abnormal ABR in 6 of the 11 newborns with congenital hypothyroidism recruited for their study which investigated the site of lesion in the auditory pathway [34].

In one double-blind placebo-controlled intervention study in school children in Benin, van den Briel et al. investigated the hearing thresholds across seven frequencies (0.25, 0.5, 1.0, 2.0, 3.0, 4.0, and 6.0 kHz) in relation to four different iodine status or biochemical concentrations: serum thyroglobulin, serum thyrotropin, serum free T4 and urinary iodine [35]. Only serum thyroglobulin concentration was found to be significantly correlated with mean hearing thresholds. Children with higher concentrations of thryroglobulin had higher hearing thresholds than those with lower concentrations of thyroglobulin and the differences were more prominent in the higher frequency range (2.0–6.0 kHz). Although median urinary iodine is considered as the main indicator of iodine status of a population, serum thyroglobulin concentration is perhaps regarded as a more sensitive indicator than thyrotropin or free thyroxine in school-aged children [25, 35].

While current evidence suggests that cognitive impairment of children living in areas of iodine deficiency may at least reverse partially, the impact of iodine deficiency on hearing thresholds following treatment remains a subject of debate. In their study of 120 school children living in endemic areas of severe iodine deficiency and 30 children living in a non-endemic area in China, Wang and Yang found that hearing impairment reversed in apparently normal children in the iodine-deficient areas 1 year after the provision of iodine prophylaxis [27]. Anand et al. investigated 20 patients with hypothyroidism before and after treatment with levothyroxine in India and found definite improvement in posttreatment audiometry and tympanometry but not with ABR. In contrast other researchers have demonstrated that hearing impairment may persist even after iodine treatment [36, 37]. Evidently, the exact mechanisms and causal relationships between iodine deficiency and various aspects of the auditory system are still not fully understood. However, the prospects of hearing impairment reversibility are higher with early treatment.

The vast majority of available studies exploring the impact of iodine deficiency on hearing impairment have been conducted among older children or adults. However, the observed hearing impairments in these studies were most likely to be congenital or of early postnatal onset considering that the adverse effects of iodine deficiency are greatest during these periods. It is also pertinent to mention that circulating maternal auto antibodies to thyroid peroxidase often linked with defective neuronal migration during the third trimester of pregnancy has also been associated with impaired auditory development. While Pendred syndrome, an autosomal recessive disorder, is commonly associated with non-endemic goiter and progressive hearing loss the mechanism is unrelated to iodine deficiency but rather to a defect in the incorporation of iodide into thyroxine molecule (iodide transport).

Iron

Iron is not only an important nutrient but also an essential element for the production of myelin and neurotransmitters such as dopamine, serotonin, and norepinephrine. This effect on the maturation of neural cells makes iron an essential component in normal neurological activity. Iron deficiency is common in pregnant women and infants worldwide and therefore constitutes a major health problem. The significance of iron deficiency on the developing brain extends well beyond the well recognized overt anemia from decreased heme proteins to neural conduction deficits as well as cognitive and behavioral disorders. Iron is an established essential substrate for normal myelin production and the immediate postnatal period is the time when uptake of iron by oligodendrocytes involved in the synthesis of

myelin is at its peak [38]. Myelin is produced from fatty acids and cholesterol and it is essential for the normal conduction of electrical signals in the central nervous system as well as the auditory system.

Although several studies have linked iron deficiency to anemia, only limited studies have explored the effects on the central nervous system [39]. Available studies link iron deficiency to delayed maturation of the ABRs and by implication hearing loss. While some researchers have reported association between iron deficiency and abnormal ABR [38, 40–42], others have reported negligible or no association [43–45]. For instance, in a study of 55 otherwise healthy 6 months old Chilean children (29 with iron deficiency anemia and 26 non-anemic controls) by Roncagliolo and colleagues, the IPL I–V or central conduction time was prolonged in the anemic group and the differences became more pronounced at 12- and 18-months follow-ups despite effective iron therapy [38]. Although the effectiveness of iron therapy in children older than 2 years is well established this group of iron-deficient infants at the age of 6 months were resistant to iron therapy suggesting a long-lasting effect of iron deficiency on brain function in early infancy.

Other studies have also linked iron deficiency anemia to delayed maturation of the auditory brainstem from increased absolute and inter-peak latencies and sometimes reduced amplitudes of the brainstem-evoked waveforms [30, 42]. In contrast, Sarici et al. investigated ABR patterns among 20 iron-deficient infants compared to their 20 age-matched controls in Turkey before and after iron supplementation [44]. They found no significant differences among the iron-deficient and control groups before and after treatment for any of the waves I, II, III, IV, and V as well as the inter-peak latencies I–III and I–V. A similar study in 2006 also from Turkey confirmed this finding in a group of iron-deficient infants with or without anemia although slight decreases in latencies were observed after treatment compared with controls [43].

Whereas postnatal iron deficiency is responsive to treatment, it appears to be long-lasting and resistant in the prenatal form. Possible pathways from available research include the direct disruption of the central conduction time and decrease in dendritic growth and aborization as well as synapse formation; or indirectly through functional regulation of neurotransmitters such as dopamine, serotonin, and γ-amino butyric acid.

The direct effect on neural conduction velocity is evident in delays from the prolongation of absolute as well as inter-peak latencies as a result of possible defects in myelin production and maintenance as demonstrated by Roncagliolo and colleagues [38]. In their study of 55 children, the late components IPL III–V from ABR waves III, IV, and V were most affected. The hypothesis that altered myelination is the most likely explanation is supported by the differences in latencies rather than amplitudes especially with late ABR components as well as the longer central conduction time which serves as an overall measure of nerve conduction velocity. Further animal studies in the myelin mutant taiep rats with electron microscopy and electrophysiologic examination demonstrated adequate myelination (Schwann cells) in the peripheral portions of the auditory nerve as well as normal responses (wave I), while the brain stem portion was completely demyelinated in adult rats.

The indirect effect of iron deficiency is evident in neurochemical abnormalities and impaired neural development especially where iron is a co-substrate. Neurotransmitters have a range of inhibitory and excitatory functions such as γ-amino butyric acid (GABA), dopamine and serotonin and phenylalanine. For instance, GABA inhibits glutamate with a regulatory effect of the hypothalamic-hypophyseal hormones responsible for behavior regulation and changes in neurotransmitter activities have been advanced as a possible explanation for the observed clinical and possibly neurological abnormalities in iron deficiency.

From the available evidence, the role of iron deficiency in hearing impairment is still a subject of debate. Evidence establishing clear pathways for instance, in support of the decrease in dendritic growth and aborization as well as synapse formation are sparse. Further human studies demonstrating causal relationship between iron deficiency and hearing impairment are required especially in populations where iron deficiency anemia is prevalent.

Zinc

Zinc is a trace element that is of vital importance for the survival and normal physiologic functioning of all living cells. It has antioxidant properties and plays an important role in cell metabolism, growth and cognitive functioning. The cochlea and vestibular labyrinths have the highest concentration of zinc while the prostrate, hair, nails, iris and cornea of the eye have lower but significant amounts. Since structures with the highest concentration of micronutrients suffer most for its deficiency, the cochlea is likely to suffer the most. However, the relationship between zinc deficiency and hearing loss remains unclear.

For example, progressive sensorineural hearing loss linked with zinc deficiency showed improvement in hearing after treatment with zinc supplement [46]. Another study of individuals with sudden sensorineural hearing loss confirmed the effectiveness of zinc therapy regardless of their hearing levels [47]. Furthermore, the protective effect of zinc on cochlea hair cells from pneumolysin- and cadmium-induced ototoxicity and its interference with the apoptotic cascade has been reported in animal studies [48]. In contrast, Hoeve and colleagues did not observe any difference in the organ of Corti or the vascular striae among rats fed with zinc deficient diet and their controls from microscopic examination of the cochlea [49]. This was consistent with the report by Wensink et al. which demonstrated that dietary zinc deficiency for up to 26 weeks had no effect on wave I–IV interval compared to zinc-adequate rats [50]. Further studies are therefore required to clarify the association and mechanism between zinc deficiency and hearing loss in humans from infancy.

Vitamin D

Vitamin D deficiency from impaired metabolism is a common cause of rickets in infants. The deficiency of calcium or phosphate in breast milk is a common cause vitamin D deficiency especially in low-income countries. It is postulated that because ionized calcium is necessary for normal nerve function vitamin D deficiency may cause sensorineural hearing loss directly or exert a secondary effect by modifying calcium metabolism [51]. For example, deficiency of ionized calcium may inhibit the release of neural transmitter substances thus adversely affecting the auditory evoked potentials of the cochlea. However, Irwin found no link between vitamin D deficiency and hearing loss in his adult patients [52]. Retro-cochlear deafness in hereditary vitamin-D-resistant rickets secondary to hyperparathyroidism causing osteosclerotic narrowing of the internal auditory canals has been reported although most of the relevant studies only established the links with hearing loss as from the age of 5 years [53, 54]. Other studies in adults with vitamin D deficiency have also reported association with hearing loss [51, 55]. Evidently, studies on the hearing profile of infants with nutritional rickets merit consideration.

Vitamin A

Although the effects of vitamin A have been extensively studied in relation to visual impairment, studies linking vitamin A deficiency directly with hearing loss in infancy are rare. However, studies have implicated vitamin A as a significant cause of acute otitis media in infants [23], while animal studies have demonstrated that vitamin A deficiency increases susceptibility to noise-induced hearing loss [56]. Both animal and human studies are required to illuminate our understanding of the specific role of vitamin A deficiency in infants with hearing loss.

Vitamin B_{12}

While vitamin B_{12} deficiency rarely occurs before the age of 4 months, it has been associated with developmental delays or disabilities in infancy and a greater risk of depression in adulthood [57]. Impact on early brain development through demyelination and inflammation which stimulates an autoimmune process that blocks intrinsic factor for cobolamin absorption have been postulated as possible pathways between vitamin B_{12} deficiency and adverse childhood development. However, the association between vitamin B_{12} deficiency and hearing impairment has not been investigated. Rather, several studies in both developed and developing countries have studied the link between vitamin B_{12} with age-related hearing loss with mixed outcomes. For example, Houston et al. found that poor auditory function was consistently associated with low concentrations of serum vitamin B_{12} and red cell folate in a sample of 55 healthy elderly women in USA even when controlled for age [58]. In contrast, one study from Nigeria only found an association between hearing loss and serum folate and not vitamin B_{12} after adjusting for age [59]. Relevant cross-cultural studies are obviously required on the full spectrum of vitamin B_{12} deficiency in infancy.

Protein-Energy Deficiencies

Previously, the term "undernutrition" was used synonymously with protein-energy malnutrition or deficiencies but now broadly used to reflect the comorbidity of undernourished physical state with micronutrient deficiencies. It is heuristic to characterize the overall nutritional status of children by comparing their growth or attained weight or height for their age (and sex) with that of a reference population of generally healthy children. The anthropometric measures for each child expressed as standard deviation scores or *z*-scores are typically categorized in nutritional terms as mild (−1.01 to −2.00 SD), moderate (−2.01 to −3.0 SD), or severe (<−3.0 SD) undernutrition. An undernourished child can be underweight, stunted and/or wasted.

Undernourished physical state resulting from protein-energy deficiencies has been associated with hearing impairment. While several studies have demonstrated independent links between specific micronutrient deficiencies and child development, the pathways for the direct impact of protein-energy deficiencies on overall child development are less clear. This is partly because the association between protein-energy malnutrition and child development is often confounded by micronutrient deficiencies and socio-economic factors especially in low-income countries. In fact, it is difficult to reliably disaggregate the effects of micronutrients from those of protein and calories in the vast majority of the available studies [60]. Notwithstanding, Ivanovic and colleagues demonstrated that undernutrition during the first year of life had long-term impact on brain development, intellectual quotient and scholastic achievement of poor high school graduates in Chile [61]. Several cross-sectional and longitudinal studies have also established association between undernutrition and cognitive, motor and behavioral development [60]. While trial studies on food supplementation showed concurrent benefits to motor development, mental development, and cognitive ability, only limited evidence exists on the sustained benefits of supplementation from pregnancy beyond the first 2 years of life [62].

Several studies have explored the effects of protein-energy malnutrition on ABR in humans [63–68], but the relationship between protein-energy malnutrition and hearing impairment has been sparsely reported [69]. Conduction delay in the proximal ABR waves in the form of prolonged IPL III to V (IPL III–V) with consistent sparing of the distal waves (IPL I–III) has been documented in available studies. By implication, the prolonged IPL III–V is also extended to the central conduction time (CCT) IPL I–V. The CCT progressively decreases after therapeutic intervention but still remains higher than that of normal controls at follow-up.

Durmaz et al. in their study of 11 infants with kwashiorkor and ten with marasmus compared with ten health controls in Turkey demonstrated significant differences among types of malnutrition [65]. The kwashiorkor group recorded the longest conduction time. This was corroborated in another study of a group of 22 children hospitalized for kwashiorkor in South Africa which showed evenly distributed abnormalities from waves I–V as well as IPL I–III, III–V, and I–V [67]. ABR abnormalities were reported as unrelated to several indices of growth retardation such as serum albumin and hemoglobin levels. Similarly, Vandana and Tandon documented prolonged latencies I, II, III, IV, I–III, and III–V in their study of 20 children with chronic malnutrition in India compared to 20 normal controls matched for age and sex [63]. They also reported lack of significant differences in the middle latency responses as well as the amplitude for waves I and V. The effects of ototoxic drugs have also been demonstrated in animal studies to be exacerbated by protein-energy deficiency [70].

Limited studies have explored the contributions of micronutrient deficiencies in the reported relationship between protein-energy malnutrition and ABR abnormalities. For example, Odabas and colleagues from Turkey reported significant conduction time difference of wave I among children with protein-energy malnutrition and iron deficiency anemia [64]. This report would suggest that iron deficiency anemia has synergistic effect on the ABR conduction time that extends to the distal portion of the waveform in the cochlea nerve. Possible explanation is that iron deficiency anemia affects the production of myelin and neurotransmitters both of which may lead to further prolongation of the conduction time to the distal portion of the ABR waveform.

Available studies especially from the developing world where the vast majority of infants are born outside hospitals are hospital-based with small sample sizes and inherent selection bias. Perhaps the only community-based study that has linked gross protein-energy malnutrition with sensorineural hearing loss is that reported from a population of 3,386 full-term infants 0–3 months old in Nigeria [69]. Infants with any undernourished physical state were significantly associated with severe-to-profound hearing loss compared to infants without any nutritional deficits. The hearing assessment protocol consisted of a first-stage test with transient evoked otoacoustic emissions (TEOAE) followed by automated auditory brainstem response (AABR) for those referred by TEOAE. TEOAE is a physiological test of the integrity of the outer hair cells in the cochlea. All those who failed AABR were scheduled for diagnostic evaluation with tympanometry, ABR, and visual response audiometry. The nutritional indices of interest were weight-for-age (WAZ), body mass index-for-age (BMI), and length-for-age (HAZ) expressed as z-scores, based on the latest Multicentre Growth Reference (MGR) of the World Health Organization (WHO). While more than half (55 %) of the infants with hearing impairment were undernourished by at least one measure of growth and development, evidence from this study also suggested that infants who suffered from any undernourished physical state whether attributable to intrauterine growth retardation, maternal problems including her nutritional status during fetal development or insults arising from infectious disease at or soon after birth were at significant risk of severe-to-profound sensorineural hearing loss very early in life. However, the contributions of micronutrient deficiencies to the observed association were not investigated. Related studies of both hospital-based and community-based cohorts from Nigeria based on WHO reference growth standards further demonstrated that full-term microcephalic infants were not only at significant risk of moderate-to-severe undernutrition compared to their normocephalic peers but also of sensorineural hearing loss regardless of whether the infants were born in or outside hospitals [71].

Overall, the relationship between undernutrition and hearing impairment in infancy remains largely uncharted and merit research attention. Population or community-based data are urgently required in low-income countries where home birth constitutes a significant risk factor or marker for severe undernutrition. Such studies must be prospective and adequately powered to discriminate among potential confounders. Community-based well child centers for routine immunization offer a possible platform for advancing what is already known on the impact of undernutrition on overall growth and development in early childhood across all key developmental domains. The growing trend towards routine newborn and infant hearing screening as a standard of newborn care should also serve to

enhance our current understanding of the complex relationship between all components of undernutrition and hearing impairment. Such information is crucial for curtailing the burden of undernutrition especially in the most disadvantaged communities in the world.

References

1. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B. International Child Development Steering Group. Developmental potential in the first 5 years for children in developing countries. Lancet. 2007;369:60–70.
2. Thompson RA, Nelson CA. Developmental science and the media: early brain development. Am Psychol. 2001;56:5–15.
3. Webb S, Monk C, Nelson C. Mechanisms of postnatal neurobiological development: implications for human development. Dev Neuropsychol. 2001;19:147–71.
4. Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol. 1997;387:167–78.
5. Morgane PJ, Austin-LaFrance R, Bronzino J, Tonkiss J, Díaz-Cintra S, Cintra L, Kemper T, Galler JR. Prenatal malnutrition and development of the brain. Neurosci Biobehav Rev. 1993;17:91–128.
6. United Nations Children's Fund (UNICEF), University of Wisconsin. Monitoring child disability in developing countries: results from the multiple indicator cluster surveys. New York: UNICEF; 2008.
7. Engel-Yeger B, Weissman D. A comparison of motor abilities and perceived self-efficacy between children with hearing impairments and normal hearing children. Disabil Rehabil. 2009;31:352–8.
8. Karchmer MA, Allen TE. The functional assessment of deaf and hard of hearing students. Am Ann Deaf. 1999;144:68–77.
9. Kennedy CR, McCann DC, Campbell MJ, Law CM, Mullee M, Petrou S, et al. Language ability after early detection of permanent childhood hearing impairment. N Engl J Med. 2006;354:2131–41.
10. Meadow-Orlans KP, Spencer PE, Koester LS, editors. The world of deaf infants: a longitudinal study. New York: Oxford University Press; 2004.
11. Ruben RJ. A time frame of critical/sensitive periods of language development. Acta Otolaryngol. 1997;117:202–5.
12. Olusanya BO, Ruben RJ, Parving A. Reducing the burden of communication disorders in the developing world: an opportunity for the millennium development project. JAMA. 2006;296(4):441–4.
13. Ruben RJ. Redefining the survival of the fittest: communication disorders in the 21st century. Laryngoscope. 2000;110:241–5.
14. Schroeder L, Petrou S, Kennedy C, McCann D, Law C, Watkin PM, Worsfold S, Yuen HM. The economic costs of congenital bilateral permanent childhood hearing impairment. Pediatrics. 2006;117:1101–12.
15. Mohr PE, Feldman JJ, Dunbar JL, McConkey-Robbins A, Niparko JK, Rittenhouse RK, Skinner MW. The societal costs of severe to profound hearing loss in the United States. Int J Technol Assess. 2000;16:1120–35.
16. World Health Organization. Neonatal and infant hearing screening. Current issues and guiding principles for action. Outcome of a WHO informal consultation held at WHO head-quarters, Geneva, Switzerland, 9–10 November, 2009. Geneva; WHO. 2010.
17. Olusanya BO, Newton VE. Global burden of childhood hearing impairment and disease control priorities for developing countries. Lancet. 2007;369:1314–7.
18. World Health Organization. Primary Ear & Hearing Care Training Resource. Advanced Level. Geneva: WHO; 2006.
19. Lieu JE, Tye-Murray N, Karzon RK, Piccirillo JF. Unilateral hearing loss is associated with worse speech-language scores in children. Pediatrics. 2010;125:e1348–55.
20. Tharpe AM. Unilateral and mild bilateral hearing loss in children: past and current perspectives. Trends Amplif. 2008;12:7–15.
21. Bess FH, Dodd-Murphy J, Parker RA. Children with minimal sensorineural hearing loss: prevalence, educational performance and functional status. Ear Hear. 1998;19:339–54.
22. World Health Organization (WHO Workgroup for development of version of ICF for Children & Youth). International Classification of Functioning, Disability and Health Children and Youth Version (ICF-CY). Geneva: WHO; 2007.
23. Elemraid MA, Mackenzie IJ, Fraser WD, et al. Nutritional factors in the pathogenesis of ear disease in children: a systematic review. Ann Trop Paediatr. 2009;29:85–99.
24. Zimmermann MB, Jooste PL, Pandav CS. Iodine-deficiency disorders. Lancet. 2008;372:1251–62.

25. World Health Organization, UNICEF, ICCIDD. Assessment of iodine deficiency disorders and monitoring their elimination: A guide for programme managers. 3rd ed. Geneva: WHO; 2007.
26. DeLong GR, Stanbury JB, Fierro-Benitez R. Neurological signs in congenital iodine-deficiency disorder (endemic cretinism). Dev Med Child Neurol. 1985;27:317–24.
27. Wang YY, Yang SH. Improvement in hearing among otherwise normal schoolchildren in iodine-deficient areas of Guizhou, China, following use of iodized salt. Lancet. 1985;2:518–20.
28. Rovet J, Walker W, Bliss B, Buchanan L, Ehrlich R. Long-term sequelae of hearing impairment in congenital hypothyroidism. J Pediatr. 1996;128:776–83.
29. Anand VT, Mann SB, Dash RJ, Mehra YN. Auditory investigations in hypothyroidism. Acta Otolaryngol. 1989;108:83–7.
30. Pharoah PO, Connolly KJ. Iodine and brain development. Dev Med Child Neurol. 1995;37:744–8.
31. DeLong GR. Iodine and brain development. Dev Med Child Neurol. 1996;38:279–82.
32. Valeix P, Preziosi P, Rossignol C, Farnier MA, Hercberg S. Relationship between urinary iodine concentration and hearing capacity in children. Eur J Clin Nutr. 1994;48:54–9.
33. Gao H, Li J, Wang E. Iodine deficiency and perceptive nerve deafness. Lin Chuang Er Bi Yan Hou Ke Za Zhi. 1998;12:228–30.
34. François M, Bonfils P, Leger J, Avan P, Czernichow P, Narcy P. Audiological assessment of eleven congenital hypothyroid infants before and after treatment. Acta Otolaryngol. 1993;113:39–42.
35. van den Briel T, West CE, Hautvast JG, Ategbo EA. Mild iodine deficiency is associated with elevated hearing thresholds in children in Benin. Eur J Clin Nutr. 2001;55:763–8.
36. Bellman SC, Davies A, Fuggle PW, Grant DB, Smith I. Mild impairment of neuro-otological function in early treated congenital hypothyroidism. Arch Dis Child. 1996;74:215–8.
37. Debruyne F, Vanderschueren-Lodeweyckx M, Bastijns P. Hearing in congenital hypothyroidism. Audiology. 1983;22:404–9.
38. Roncagliolo M, Garrido M, Walter T, Peirano P, Lozoff B. Evidence of altered central nervous system development in infants with iron deficiency anemia at 6 mo: delayed maturation of auditory brainstem responses. Am J Clin Nutr. 1998;68:683–90.
39. Grantham-McGregor S, Baker-Henningham H. Iron deficiency in childhood: causes and consequences for child development. Ann Nestlé [Engl]. 2010;68:105–19.
40. Algarín C, Peirano P, Garrido M, Pizarro F, Lozoff B. Iron deficiency anemia in infancy: long-lasting effects on auditory and visual system functioning. Pediatr Res. 2003;53:217–23.
41. Cankaya H, Oner AF, Egeli E, Caksen H, Uner A, Akçay G. Auditory brainstem response in children with iron deficiency anemia. Acta Paediatr Taiwan. 2003;44:21–4.
42. Shankar N, Tandon OP, Bandhu R, Madan N, Gomber S. Brainstem auditory evoked potential responses in iron-deficient anemic children. Indian J Physiol Pharmacol. 2000;44:297–303.
43. Kürekçi AE, Sarici SU, Karaoglu A, Ulaş UH, Atay AA, Serdar MA, Akin R, Ozcan O. Effects of iron deficiency versus iron deficiency anemia on brainstem auditory evoked potentials in infancy. Turk J Pediatr. 2006;48:334–9.
44. Sarici SU, Serdar MA, Dündaröz MR, Unay B, Akin R, Deda G, Gökçay E. Brainstem auditory-evoked potentials in iron-deficiency anemia. Pediatr Neurol. 2001;24:205–8.
45. Ozturan O, Henley CM, Littman TA, Jenkins HA. Iron deficiency anemia and hearing. ORL J Otorhinolaryngol Relat Spec. 1997;59:73–8.
46. Shambaugh Jr GE. Zinc: the neglected nutrient. Am J Otol. 1989;10:156–60.
47. Yang CH, Ko MT, Peng JP, Hwang CF. Zinc in the treatment of idiopathic sudden sensorineural hearing loss. Laryngoscope. 2011;121:617–21.
48. Agirdir BV, Bilgen I, Dinc O, Ozçağlar HU, Fişenk F, Turhan M, Oner G. Effect of zinc ion on cadmium-induced auditory changes. Biol Trace Elem Res. 2002;88:153–63.
49. Hoeve LJ, Wensink J, Mertens zur Borg IR. Hearing loss related to zinc deficiency in rats. Eur Arch Otorhinolaryngol. 1990;247:267–70.
50. Wensink J, Hoeve H, Mertens zur Borg I, Van den Hamer CJ. Dietary zinc deficiency has no effect on auditory brainstem responses in the rat. Biol Trace Elem Res. 1989;22:55–62.
51. Brookes GB. Vitamin D, deficiency and deafness: 1984 update. Am J Otol. 1985;6:102–7.
52. Irwin J. Hearing-loss and calciferol deficiency. J Laryngol Otol. 1986;100:1245–7.
53. Weir N. Sensorineural deafness associated with recessive hypophosphataemic rickets. J Laryngol Otol. 1977;91:717–22.
54. Stamp TC, Baker LR. Recessive hypophosphataemic rickets, and possible aetiology of the ‘vitamin D-resistant’ syndrome. Arch Dis Child. 1976;51:360–5.
55. Ikeda K, Kobayashi T, Itoh Z, Kusakari J, Takasaka T. Evaluation of vitamin D metabolism in patients with bilateral sensorineural hearing loss. Am J Otol. 1989;10:11–3.
56. Biesalski HK, Wellner U, Weiser H. Vitamin A deficiency increases noise susceptibility in guinea pigs. J Nutr. 1990;120(7):726–37.

57. Black MM. Effects of vitamin B12 and folate deficiency on brain development in children. Food Nutr Bull. 2008;29(2 Suppl):S126–31.
58. Houston DK, Johnson MA, Nozza RJ, Gunter EW, Shea KJ, Cutler GM, Edmonds JT. Age-related hearing loss, vitamin B-12, and folate in elderly women. Am J Clin Nutr. 1999;69:564–71.
59. Lasisi AO, Fehintola FA, Yusuf OB. Age-related hearing loss, vitamin B12, and folate in the elderly. Otolaryngol Head Neck Surg. 2010;143:826–30.
60. Grantham-McGregor S, Baker-Henningham H. Review of the evidence linking protein and energy to mental development. Public Health Nutr. 2005;8:1191–201.
61. Ivanovic DM, Leiva BP, Perez HT, Inzunza NB, Almagià AF, Toro TD, Urrutia MS, Cervilla JO, Bosch EO. Long-term effects of severe undernutrition during the first year of life on brain development and learning in Chilean high-school graduates. Nutrition. 2000;16:1056–63.
62. Walker SP, Wachs TD, Gardner JM, Lozoff B, Wasserman GA, Pollitt E, Carter JA. International Child Development Steering Group. Child development: risk factors for adverse outcomes in developing countries. Lancet. 2007;369:145–57.
63. Vandana, Tandon OP. Auditory evoked potential responses in chronic malnourished children. Indian J Physiol Pharmacol. 2006;50:48–52.
64. Odabaş D, Caksen H, Sar S, Tombul T, Kisli M, Tuncer O, Yuca K, Yilmaz C. Auditory brainstem potentials in children with protein energy malnutrition. Int J Pediatr Otorhinolaryngol. 2005;69:923–8.
65. Durmaz S, Karagöl U, Deda G, Onal MZ. Brainstem auditory and visual evoked potentials in children with protein-energy malnutrition. Pediatr Int. 1999;41:615–9.
66. Flinn JM, Barnet AB, Lydick S, Lackner J. Infant malnutrition affects cortical auditory evoked potentials. Percept Mot Skills. 1993;76:1359–62.
67. Bartel PR, Robinson E, Conradie JM, Prinsloo JG. Brainstem auditory evoked potentials in severely malnourished children with kwashiorkor. Neuropediatrics. 1986;17:178–82.
68. Barnet AB, Weiss IP, Sotillo MV, Ohlrich ES, Shkurovich M, Cravioto J. Abnormal auditory evoked potentials in early infancy malnutrition. Science. 1978;201:450–2.
69. Olusanya BO. Is undernutrition a risk factor for sensorineural hearing loss in early infancy? Br J Nutr. 2010;103:1296–301.
70. Lautermann J, Schacht J. Nutritional state is a risk factor for drug-induced ototoxicity. Laryngorhinootologie. 1995;74:724–7.
71. Olusanya BO. Risk of sensorineural hearing loss in infants with abnormal head size. Ann Afr Med. (in press).

Chapter 16
Nutritional Management of Diabetes Mellitus in Infants and Children

Ruth M. Ayling

Key Points

- Children with diabetes have essentially the same nutritional requirements as other children
- Nutritional recommendations should include healthy eating practices for the whole family, taking into account its culture, habits and customs
- Frequent dietetic review should take place to take account of changes in dietary requirements and habits with age
- Nutritional management should be tailored to the child's insulin regimen and should include specific advice to cover exercise and intercurrent illness

Keywords Diabetes mellitus • Insulin • Nutritional requirements

Introduction

Diabetes mellitus is the most common metabolic disease of childhood and is characterised by a defect in the secretion or action of insulin. Deficiency of insulin at tissue level results in abnormalities in the metabolism of carbohydrate, protein and lipid. Diabetes is diagnosed on the basis of blood glucose criteria and the presence or absence of typical symptoms such as polyuria, polydipsia, and weight loss [1] (Table 16.1). In the absence of symptoms more than one blood glucose result is required in order to make a diagnosis.

Classification of Diabetes

Diabetes mellitus is not a single entity and can be classified according to aetiology [2] (Table 16.2). This classification has important implications with respect to subsequent management of the condition.

Type 1 is the most common form of diabetes in childhood. Onset is typically acute with characteristic diabetic symptoms and if untreated may progress to ketoacidosis, coma and death; treatment

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Table 16.1 Criteria for the diagnosis of diabetes mellitus

Random plasma glucose ≥11.1 mmol/L in the presence of typical symptoms
Fasting plasma glucose ≥7.0 mmol/L
Plasma glucose ≥11.1 mmol/L at 2 h post glucose load during oral glucose tolerance test

Table 16.2 Classification of diabetes mellitus in childhood

Type 1
β-cell destruction leading to insulin deficiency
Type 2
Insulin resistance with relative insulin deficiency
Other specific types
Genetic defects of β-cell function, e.g. MODY
Genetic defects in insulin action, e.g. Rabson–Mendenhall syndrome
Disease of the exocrine pancreas, e.g. cystic fibrosis
Endocrinopathies, e.g. Cushing's syndrome
Drug induced, e.g. glucocorticoids, α-interferon
Infections, e.g. congenital rubella
Uncommon immune-mediated forms, e.g. anti-insulin receptor antibodies, polyendocrine auto-immune deficiencies (APS I and II)
Other genetic syndromes associated with diabetes mellitus, e.g. Wolfram, Prader–Willi

is with insulin. The incidence of Type 1 is increasing; the EURODIAB study showed a 3.2% annual increase for 1989–1998 and a 3.9% increase for 1989–2003, with the highest increase in incidence in children under five years of age [3]. However, at present only about 4% of children with Type 1 diabetes are under 2 years of age. Neonatal diabetes is very rare with an incidence of about 1 in 400,000. Many cases are transient and associated with parental disomy and imprinting defects of chromosome 6 [4].

Type 2 diabetes occurs where there is insufficient insulin secretion to meet increased requirements secondary to insulin resistance. It is often seen in association with other aspects of insulin resistance such as obesity, dyslipidaemia, hypertension, acanthosis nigricans and non-alcoholic fatty liver disease. Whilst it is being recognised with increasing frequency in childhood and adolescence [5], it is rare before the second decade of life. The major nutritional consideration is correction or limitation of obesity. It is important to differentiate type 2 which often does not require insulin treatment and MODY, a group of monogenetic forms of diabetes from Type 1. MODY2, caused by defects in glucokinase is the form most likely to affect younger children. It causes a mildly raised blood glucose concentration, typically 5.5–8.5 mmol/L. In this condition the glucose is regulated at a higher "set point" which tends not to be associated with complications hence these children do not require treatment.

Aims of Nutritional Management

The aims of nutritional management of diabetes are presented in Table 16.3.

Initial dietary advice should be provided to young children and their careers as soon as is practicable after diagnosis, by a dietician with specific training in paediatric diabetes. At this consultation simple advice should be given within the context of the family's specific eating habits and customs. The child's usual food intake, specific likes and dislikes and meal times should be discussed, together with relevant weekly activities, for example attendance at nursery or swimming lessons. A further appointment should be arranged for more detailed discussion, with follow-up as necessary in order to

Table 16.3 Aims of nutritional management of diabetes

To improve health through healthy food choices and appropriate physical activity
To address individual nutritional needs, considering personal and cultural preferences and lifestyle
To provide sufficient and appropriate energy and nutrients for optimal growth, development and health
To achieve and maintain: blood glucose concentrations in the normal range
An appropriate body mass index
An optimal lipid profile
Normal blood pressure
To reduce the risk of micro- and macro-vascular complications
To maintain quality of life

Table 16.4 Energy intake recommendations in diabetes mellitus in infants and children

Daily energy intake should be:
Carbohydrate 50–55%
Sucrose up to 10% of total
Fat 30–35% (up to 40% in first 2 years of life)
>10% Monounsaturated fat (up to 20% of total)
<10% Saturated fat +trans fatty acids
<10% Polyunsaturated fat
Protein 10–15%
Decreasing from 2 g/kg body weight in early infancy

deal with changes in the child's growth and eating and exercise patterns and any specific dietary issues that may arise.

Guidelines on Energy Balance and Individual Food Components

There is relatively little research looking specifically at nutritional requirements in children with diabetes and current guidance is largely consensus based [6, 7] using principles drawn from knowledge of general dietary requirements [8] and nutritional management of adults with diabetes [9, 10]. This means that any dietary recommendations are suitable for the whole family who should ideally all be involved in making improvements to their diet based on healthy eating principles. Energy intake recommendations are given in Table 16.4. Five portions of fruit or vegetables a day are also recommended [11].

Carbohydrate

Carbohydrate should form 50–55% of daily energy intake. The glycaemic index is a ranking of foods based on their acute glycaemic index compared to glucose. Carbohydrates with a low glycaemic index, such as wholegrain breads, pasta and low fat dairy products, cause a more gradual, less pronounced rise in blood glucose than those with a high glycaemic index and are preferred dietary sources. In children denial of sucrose containing foods can be difficult and they can be used in the diet

in moderation, although sucrose-sweetened drinks have been noted to cause hyperglycaemia and have been associated with weight gain so are best avoided.

For children above the age of one year a daily dietary fibre content of 2.4–3.4 g/mJ is recommended. A more practical approach is that the fibre requirement (g/day), for children over 2 years is age in years +5.

Fat

Fat should be limited to 30–35% of energy intake in older children, although infants and children up to 2 years may derive 40% of their energy intake from fat. Saturated fat, found in fatty meats, full fat dairy products and high fat snack food should be reduced with a relative increase in polyunsaturated and monounsaturated fat. Note that the use of reduced fat milk is not recommended for children under 2 years of age as it is lower both in energy and fat soluble vitamin content than whole milk. Sources of polyunsaturated fat include sunflower oil and oily fish. Ten to twenty percent of energy should be derived from monounsaturated fat, for example in olive and sesame oil, nuts and peanut butter.

Protein

Protein requirements fall during childhood, being highest in infancy. During childhood years protein should comprise 10–15% of total energy intake. Suitable sources include legumes, fish, lean meat and low fat dairy products.

Trace Elements

Recommendations for vitamin and mineral consumption in infants and children with diabetes do not differ from those of other children [8].

Salt

Salt intake is associated with hypertension and limitation of intake to less than 6 g/day is advised in all adults, particularly those with diabetes. Recommended maximum salt intakes for children are lower being <1 g/day until 1 year, <2g/day from 1 to 2 years and <3g/day from 4 to 6 years of age [12]. Dietary advice should be given regarding choice of low salt products and not adding salt to meals.

"Diabetic" Foods

The use of proprietary "diabetic" foods is discouraged. It should be possible to eat normally and healthy without recourse to such items which tend to be high in fat and sweet tasting, thus encouraging unhealthy eating habits.

Artificial Sweeteners

These are sometimes classified as nutritive and non-nutritive. Nutritive sweeteners, such as fructose and the sugar alcohols sorbitol and xylitol, are only partially absorbed and excessive use will cause diarrhoea. Non-nutritive sweeteners include aspartame, saccharin and acesulfame K. Their consumption in products such as diet drinks and low fat dairy products does not affect glycaemic control and is acceptable in moderation.

Nutrition Advice for Different Insulin Regimens and Specific Circumstances

In Western nations about 90% of childhood diabetes is Type 1. Acquired forms of diabetes are less likely to occur in infants and young children than in older children and adolescents. Immediately after diagnosis with Type 1, children may experience a "honeymoon period" during which insulin requirements are low and it is relatively easy to maintain good glycaemic control. After this, as insulin requirements increase, more intensive regimens may be required to achieve the same degree of glycaemic control. The twice daily injections using a combination of short/rapid and intermediate acting insulin before breakfast and the evening meal can be used in young children. Three meals and three snacks are recommended to ensure optimal glycaemic control and daily carbohydrate consumption should be reasonably consistent. Treatment of hypoglycaemia should be with short acting carbohydrate followed by a longer acting form. Older children may achieve better control using three injections—a mixture of short/rapid and intermediate before breakfast, short/rapid before the evening meal and intermediate acting in the evening. More intensive diabetes management may be achieved using multiple daily injections with a basal dose of long-acting insulin and rapid acting insulin before meals although tends to be used more in teenagers whose daily routine is more variable than that of younger children. It allows greater flexibility in meal timing and quantities although requires an ability to adjust insulin dose according to the carbohydrate content of the meal. Snacks between meals are not a necessity and only short acting carbohydrate is required to treat hypoglycaemia. An alternative to this is continuous subcutaneous infusion (insulin pump therapy) in which a continuous subcutaneous infusion of basal insulin is given with bolus doses to match carbohydrate eaten. Insulin pumps have been used successfully, even in very small children and babies.

Exercise

Children with diabetes should be encouraged to participate in regular exercise to promote cardiovascular health and aid achievement or maintenance of an optimal body weight. Many older children with diabetes engage in physical training and competitive sports. For younger children exercise is often part of their normal daily activity and can be managed accordingly. Addition, anticipated regular exercise such as weekly football practice may be able to be accommodated by a change in meal plan and reduction in insulin dose on that day. Unplanned exercise should be managed by use of short-acting carbohydrate, careful monitoring of blood glucose and subsequent reduction of long-acting insulin if necessary to prevent delayed hypoglycaemia.

Illness

Young children are prone to frequent intercurrent illnesses. These can make diabetes hard to manage, particularly if accompanied by nausea or vomiting. Specific advice to parents includes continued administration of insulin, monitoring of blood glucose and testing for the presence of ketones. Dietary management involves provision of regular carbohydrate, if necessary as small frequent snacks rather than larger meals.

Age-Specific Advice

Infants

Exclusive breastfeeding is recommended, with weaning in line with general recommendations for infants [13]. Infants whose mothers have chosen not to breast feed should be given an appropriate formula milk. Regular feeding, for example every 3–4 h will help maintain euglycaemia. The diagnosis of diabetes in very young children poses particular management problems and great concerns for parents and carers. Infants do not exhibit classical catecholamine responses to hypoglycaemia not are they able to easily communicate any sensations associated with hypoglycaemia that they do experience. Hypoglycaemia is therefore particularly feared in this age group. In addition, as the brain of young children is still developing the adverse risk of hypoglycaemia is potentially greater than in older children. Some consider less strict glycaemic control is appropriate in this age group and in preschool children [14]. However, there is some evidence that hyperglycaemia may impair cognitive performance [15], reinforcing the need for good glycaemic control.

Toddlers

In toddlers dietary management may be problematic as tantrums, "pickiness" and food refusal are common. As relaxed an approach to mealtimes as is possible should be adopted so that negative food-related behaviours are not reinforced. Carbohydrate should be substituted for any food refused but not in the form of snack food.

Young Children

Young children can begin to participate in aspects of their own diabetes care such as helping with aspects of blood glucose testing and can begin to understand their dietary needs. At this age they begin to spend time away from their own home at nursery, school and with friends. All those involved in the care of a child with diabetes will need to be educated about the condition and its treatment and dietary management.

The major role of nutritional management in diabetes in infants and young children is in the treatment of those who have type 1 diabetes and are insulin dependent. The fundamental principles of nutrition do not differ from those of other children, although there is less flexibility with respect to timing of meals and dietary carbohydrate content. In younger children food intake tends to be erratic

at times due to behavioural issues and intercurrent illness and hypoglycaemia is harder to recognise making management more difficult.

References

1. World Health Organisation. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. WHO/NCD/NCS/99.2. Geneva. Ref Type Report. 1999.
2. Craig ME, Hattersley A, Donaghue KC. Definition, epidemiology and classification of diabetes in children and adolescents. ISPAD clinical practice consensus guidelines 2009 compendium. Pediatr Diabetes. 2009;10 (Suppl12):3–12.
3. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G, EURODIAB Study Group. Incidence trends for childhood type 1diabetes in Europe during 1998–2003 and predicted new cases 2003–20:a multicentre study. Lancet. 2009;373:2027–33.
4. Greeley SA, Tucker SE, Naylor RN, Bell GI, Philipson LH. Neonatal diabetes mellitus: a model for personalized medicine. Trends Endocrinol Metab. 2010;21:464–72.
5. Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. J Pediatr. 2005;146:693–700.
6. NICE Type 1 diabetes diagnosis and treatment of type 1 diabetes in children and young people, 2004 www.nice.org.uk/pdf/type1/diabetes. Accessed 13 Aug 2011.
7. Smart C, Aslander-van Vliet E, Waldron S. Nutritional management in children and adolescents with diabetes, ISPAD clinical practice consensus guidelines. Pediatr Diabetes. 2009;10 Suppl 12:100–17.
8. Department of Health. Dietary reference values for food energy and nutrients for the United Kingdom. Report of the panel on dietary reference values of the committee on medical aspects of food policy. Rep Health Soc Subj (Lond). 1991;41:1–20.
9. Franz MJ, Bantle JP, Beebe CA, et al. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. Technical review. Diabetes Care. 2002;25:148–98.
10. American Diabetes Association. Evidence based nutrition principles and recommendations in diabetes (position statement). Diabetes Care. 2003;26 Suppl 1:S51–61.
11. Department of Health. At least 5 a day. Strategies to increase vegetable and fruit consumption.1997. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4008049 .Accessed 12 Aug 2011.
12. Scientific Advisory Committee on Nutrition. Salt and health. London TSO 2003.
13. Fewtrell M, Wilson DC, Booth I, Lucas A. Six months of exclusive breast feeding: how good is the evidence? BMJ. 2010;342:c5955.
14. Silverstein J, Klingensmith K, Copeland L, Plotnick L, Kauffman F, Laffel L, Deeb L, Grey M, Anderson B, Holzmeister LA, Clark W. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care. 2005;28:186–212.
15. Gonder-Fredrick LA, Zrebiec JF, Bauchowitz AV, Ritteband LM, Magee JC, Cox DJ, Clarke WL. Cognitive function is disrupted by both hypo and hyperglycemia in school-aged children with type 1 diabetes: a field study. Diabetes Care. 2009;32:1001–6.

Chapter 17
Nutritional Considerations for Infants and Children During Critical Illness and Surgery

Joyce L. Owens, Sheila J. Hanson, and Jennifer McArthur

Key Points

- Children are susceptible to the negative consequences associated with a prolonged metabolic response to stress.
- Resting energy expenditure in critically ill children may vary but is predominantly hypometabolic.
- The optimal energy, protein, and nutrient requirements in critically ill children are unknown.

Keywords Metabolic response • Metabolic response to stress • Critical illness • Surgery • Cytokines • Critical illness • Immunoparesis • Malnutrition • Obesity • Nutrition assessment • Energy requirements • Resting energy expenditure • Pharmaconutrition • Macronutrients and micronutrients • Antioxidants • Nutrition support

Introduction

This chapter provides a basic overview of the metabolic response to stress. A considerable amount of knowledge regarding the metabolic response to stress has been obtained by studies in adults. Many factors are involved in the physiological response to stress, thereby impacting nutritional needs throughout this phase of illness. Current interest has propelled studies in pediatrics identifying unique characteristics of this response during critical illness and in several forms of surgery including general, cardiac, and minimally invasive surgery (MIS).

Children have different age-related nutrient and energy requirements than adults due to their need for growth and development. Although there are many nutritional screening tools designed to identify individuals at nutritional risk, only a few have been validated. Predictive equations are used extensively to determine energy requirements in adults and children but are highly prone to both over and underestimating of energy requirements in the hospitalized patient [1, 2]. While better knowledge on optimal energy requirements during critical illness is needed, there is an even greater paucity of data regarding the optimal macronutrient and micronutrient needs in critical illness. Pharmaconutrition is the study of the pharmacologic benefits of therapeutic use of specific nutrients in various disease

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states and trauma. This is an emerging area of research. Despite the obvious importance of providing nutrition during critical illness, there are numerous barriers to initiating and sustaining nutritional support. These will be reviewed.

Metabolic Response to Stress: Overview

Stress is defined as a disruption of the body's homeostasis [1]. In response to stress the human body initiates sequential responses termed the metabolic response to stress. This response is aimed at dealing with noxious stimuli that could potentially alter health and well-being. Noxious stimuli may include, but are not limited to, infection, trauma, and/or surgery. Infants, children, and adults all experience the metabolic response to stress, though it varies somewhat in the different age groups [1].

Over the past 20 years there has been a substantial increase in the knowledge and awareness of the metabolic response during critical illness, trauma, and surgery. Short-term response to stress in the human body is beneficial, but prolonged stress may actually cause harm. Increased knowledge has facilitated ongoing changes in medical practices, treatment, and research to minimize the potential detrimental effects that can occur. During prolonged periods of stress, infants and young children, more so than adults, are particularly susceptible to the detrimental effects of stress [2–4].

Cytokines are chemical messengers that regulate both local and systemic immune function and are initiated by nuclear factor kappa β (NF-kβ) [1, 5]. Cytokines play an integral role in regulation of the inflammatory response to stress, infection, trauma, and surgery. Various types of cytokines have been identified and characterized as anti-inflammatory, proinflammatory, or both. Upon release into the circulatory system, cytokines exhibit autocrine and paracrine functions as well as modulation of gene expression in specific cells [1].

The initiation of cytokine production alters macronutrient metabolism (protein, carbohydrate, and lipid). Short term, this is an adaptive mechanism. Once the body's limited glycogen stores are depleted through glycogenolysis, gluconeogenesis ensues. Gluconeogenesis is the provision of energy from a nonglucose source (protein, fat) and associated with elevated levels of catecholamines (epinephrine, norepinephrine, dopamine) and counterregulatory hormones (cortisol, glucagon). This results in insulin resistance and decreased levels of growth hormones. This in turns provokes catabolism of skeletal muscle (Fig. 17.1, Metabolic Response) [6, 7]. The catabolism of muscle results in mobilization of free amino acids. This mobilization yields a decreased synthesis of structural proteins such as albumin

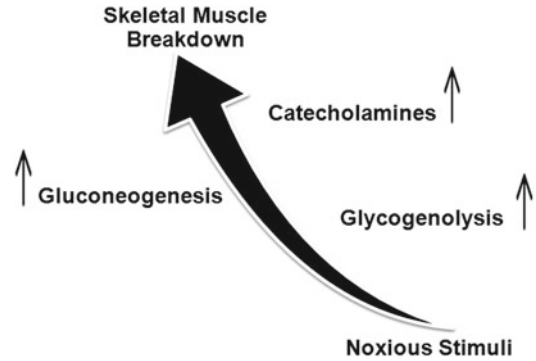

Fig. 17.1 Metabolic response overview of the pathway to skeletal muscle breakdown

and other protein constituents required for tissue repair. As a consequence, there is increased synthesis of nonstructural proteins, such as C-reactive protein, fibrinogen, enzymes, cytokines, and production of glucose via gluconeogenesis [2, 4, 7]. Prolonged skeletal muscle catabolism can result in negative consequences especially in infants and young children due to their limited muscle (protein) reserves. This can potentially lead to respiratory and heart muscle compromise. Due to the elevated levels of catabolic hormones (catecholamines and counterregulatory), growth is halted during this phase. Approximately one-third of energy needs in infants are for growth.

Contrary to starvation, providing exogenous glucose or excessive energy does not halt these mechanisms but instead excessive amounts generate lipogenesis. Providing exogenous protein has a major role in minimizing muscle protein loss but does not halt the metabolic process and a negative protein balance continues [3].

General Characteristics of Metabolic Response in Critical Illness

Proinflammatory cytokines that are in the body in increased levels during sepsis, trauma, and the postperative period promote increased lipolysis of adipose tissue but may alter lipase function [8]. Excessive lipid administration may result in impairment of leukocyte and platelet function, impaired pulmonary function, and hypertriglyceridemia. Consequences are an increase in serum fatty acids, fatty liver, tachypnea, and hypercarbia. Little data is available depicting the ability of infants to oxidize lipids during critical illness or sepsis [8].

The type of anesthetic agents used during surgery or in critical illness helps offset the metabolic response to stress. For example, the opioid anesthetic fentanyl has been shown not only to decrease muscle protein breakdown but also to reduce the postoperative endocrine stress response thereby blunting the intensity of the physiological response to stress [1].

General Characteristics of Metabolic Response After Surgery

Surgical stress induces the inflammatory response as outlined in the metabolic response to stress overview. A portion of the cytokines or chemical mediators generated during the response are derived from the surgical wound as a direct result of local cellular injury followed by release of cytokines into the systemic circulation [1].

Stimulation of the immune response is thought to eliminate opportunistic microbial organisms while immuneparesis reduces this immune response initiating the healing phase. The metabolic response to surgery is also impacted by the extent of fasting prior to surgery. Fasting prior to surgery exaggerates the stress response which is accompanied by an increased level of insulin resistance postoperatively [1].

Numerous fluctuations in the metabolic response to stress and its consequences fluctuate by age [1, 2]. An attenuated immune response is seen in surgical neonates less than 48 h old in comparison to an older infant or young child. Adolescents tend to have a longer duration of metabolic stress response than infants and young children. One possible explanation for the lessened response in the younger infant is the higher synthesis of intrinsic opioids during the perinatal period thereby blunting the metabolic response. This theory is further supported by the presence of the inflammatory cytokine interleukin-6 (IL-6) seen in older children but not in neonates [1].

Infants and young children have an increased surface area (body and head) in comparison to bodyweight. Such factors place them at greater risk for dissipation of body heat compared to adults. What protects adults and older children from hypothermia is brown fat. The predominant role of brown fat

is thermogenesis. The lack of brown fat compared to adults contributes to heat loss in infants. Also, during surgery decreased heat production is noted, yielding a lower body core temperature. This may be related to several factors modulating thermoregulation such as anesthetic medications or open body cavities. Both muscle relaxants and anesthesia impede the body's ability to generate heat through shivering, thus the increase in energy expenditure generated through shivering is insignificant during surgery [1, 4].

Interleukin-6 (IL-6) is the most consistently elevated postoperative cytokine identified in the postoperative period in adults, older infants, and children, although it is not detected after all types of surgeries. Prolonged elevated levels of IL-6 can occur due to complex infections or surgeries. IL-6 levels appear to peak 6–24 h after surgery and return to baseline generally by postoperative day 2. Diminished or the complete absence of IL-6 levels are associated with minor surgeries. The metabolic response including level of acute phase reactants, immune and endocrine response is proportional to the magnitude of surgery. Reducing postoperative metabolic derangements may help minimize postoperative complications [1]. Stimulation of the immune response is thought to eliminate opportunistic microbial organisms while a period of decreased immunological challenge referred to as immunoparesis reduces this immune response (stimulation) to initiate the healing phase [1].

Tumor necrosis factor-alpha (TNF-α) is a potent mediator in the stress response. It is rarely detected in minor or uncomplicated surgeries. However, a wide variety of levels have been found in major surgeries. Elevated levels in infants correlate with severity of surgery and likelihood of death [1].

Cardiac Surgery

Postoperatively, elevated IL-10 levels are seen in moderate and severe surgical stress. IL-10 is a potent immune-suppressive cytokine. In pediatric cardiac surgical patients IL-10 is particularly elevated. The elevated levels are observed after the start of bypass and generally decline to postoperative levels 2–3 days after surgery [1]. Elevated levels have been demonstrated to correlate with surgery severity and likelihood of death. Following cardiopulmonary bypass neonates are at risk for an exaggerated inflammatory response. The exaggerated response is manifested by capillary leak syndrome, general edema, and multisystem organ dysfunction (MOD). Subsequently, modified ultrafiltration (MUF), a unique form of continuous renal replacement therapy is utilized to extract cytokines thereby attenuating the inflammatory response. Despite the inflammatory state seen in cardiopulmonary bypass (CPB), children also develop impaired immune function after CPB. Following CPB there is evidence that children with monocyte hypofunction have a greater risk for sepsis [9].

Minimally Invasive Surgery

Significant elevation in circulating levels of TNF-α does not generally accompany minimally invasive surgery (MIS). Examples of MIS surgery include minimally invasive cardiac surgery and laparoscopy. MIS inflicts less surgical trauma and subsequently has the potential to decrease the intensity of the metabolic response to stress. MIS may also modulate thermoregulation especially in infants and young children as it alleviates the need to open body cavities and the subsequent loss of body heat. Unfortunately, current data reveals conflicting results. Some studies have found no sizable reduction in the levels of cytokines post-MIS compared to traditional surgical techniques. The majority of studies showing a reduction of cytokines levels to date have been in major surgeries. There is a theoretical concern that this downregulation of the metabolic response could potentially lead to the healing mechanism not being effectively initiated [1]. See Fig. 17.2 for an overview of the cytokine profile following surgery.

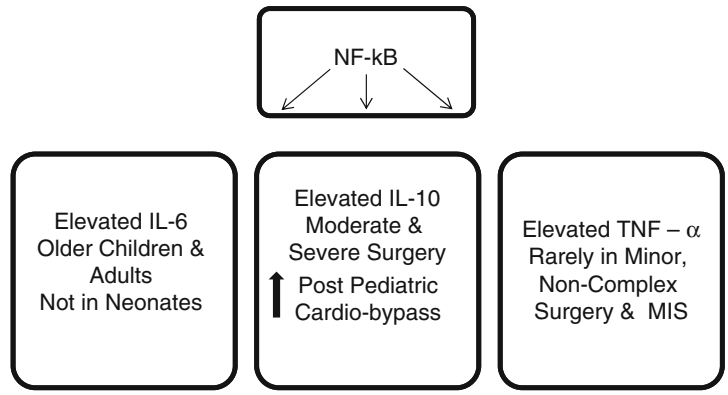

Fig. 17.2 Postoperative Cytokine Profile of Infants, Children and Adults NF-κB = nuclear factor kappa B, IL = interleukin, TNF-α = tumor necrosis factor alpha, MIS = minimally invasive surgery, ↑ = markedly elevated

Additional Considerations During Pediatric Critical Illness

Malnutrition

Critically ill infants and children with preexisting acute or chronic disease are at increased risk for malnutrition and MOD [10]. Hospitalized children (44%) with a variety of acute and chronic diseases may develop malnutrition [7]. Malnutrition facilitates physiologic aberrations with subsequent gastrointestinal alteration, immune impairment (cell mediated and phagocytosis), and the imbalance of micronutrients. A higher incidence of protein-energy malnutrition (PEM) occurs in children with congenital heart disease. Risk factors leading to PEM are energy deficits associated with increased work of breathing and/or cardiac failure; malabsorption as a consequence of lower cardiac function, elevated right-side heart pressure, and/or impaired gastrointestinal function accompanied by decreased intake [7]. Depletion of endogenous antioxidants during oxidative stress is another possible contributing factor in the development of MOD during critical illness [5], by the initiation of reactive oxygen species following ischemia or reperfusion injury [11].

Burns

Burn injury induces a considerable metabolic response to stress. The degree of response directly correlates with the size of injury up to a plateau of 40% of total body surface area burn. The metabolic response to burns is increased proteolysis, nitrogen loss, and lipolysis induced by the upregulation of catabolic hormones including catecholamines, glucagon, and cortisol. The elevation of acute phase reactants catecholamines, and cytokines has been shown in the severely burned pediatric patient to endure up to 3 years postinjury [12]. The inflammatory response initiated by burns is not restricted to the local wound. Burns affect such organs as the gastrointestinal tract causing gut permeability and a suppression of immune function through decrease synthesis and function of neutrophils, macrophages, and T-lymphocytes through impaired phagocytosis. Critically ill children with burns are also at risk of malnutrition, loss of muscle mass, and infections [10, 13]. Children who have suffered burn injury and inhalation injury have increased mortality. As the pediatric burn patient's length of time in the pediatric intensive care unit (PICU) increases so their their for a cumulative energy deficit. Factors independent of the length of stay contributing to this energy deficit involve length of mechanical ventilation and required surgical interventions [7].

In severe burns, protein catabolism is extensive leading to a negative nitrogen balance as well as loss of muscle mass partially related to cortisol. Anabolic hormones crucial to protein synthesis such

as insulin-like growth factor (IGF-1) and growth hormone are reduced following significant burn injury. Protein synthesis plus wound healing requires a positive nitrogen balance. Tachycardia and lipolysis may persist leading to fatty liver infiltration and cardiac failure. A decrease in lean body mass has been confirmed to ensue up to 1 year following injury and impediment of linear growth has been described up to 2 years following injury [7]. In a randomized control trial involving 205 severely burned pediatric patients over a 9-year period, the patients that received recombinant human growth (rhGH) demonstrated higher lean body mass, reduced scarring, and an attenuated inflammatory response. In another study involving 180 severely burn pediatric patients with ≥40% TBSA, females were found to have attenuated inflammatory response in contrast to males. Insulin therapy has proven to be of benefit to severely burn pediatric patients in which hyperglycemia is a hallmark finding. In a prospective randomized trial, 239 pediatric patients with burns >30% TBSA were randomized to receive intensive insulin therapy (IIT). Compared to controls, the IIT group had less insulin resistance, and sepsis attenuated inflammatory response measured by decreased levels of IL-6 and demonstrated improved organ function. The mortality rate for the IIT group was 4% compared to the controls at 11% [14].

Pediatric Obesity

Pediatric obesity is considered an epidemic worldwide. Despite this, the pediatric obese critically ill child has not been intensively studied. Higher complication rates appear to manifest in the critically ill obese child and adolescent as longer mechanical ventilation days and prolonged PICU stays compared to lean pediatric trauma patients [10, 15]. In addition, obese children have altered polyunsaturated fatty acid (PUFA) levels (low ω-3 PUFA to ω-6 PUFA ratio). It is unknown if this may contribute to a heightened inflammatory response during critical illness [10]. Obese individuals have a higher distribution of white adipose (fat) tissue (WAT). WAT is comprised of adipocytes, endothelial cells, fibroblasts, leukocytes, and macrophages. WAT is characterized as both an endocrine and paracrine organ, and as such is a mediator in metabolism and inflammation. The role of WAT is to store and mobilize fat for body energy and secrete hormones termed adipokines or adiopocytokines. These cells secrete various types of cytokines, adiponectin, growth factors, leptin, TNF-α, etc. Adiponectin increases the sensitivity of the liver and muscle to insulin, and adiponectin levels are depressed in obesity. Inflamed adipose tissue enhances insulin resistance [16]. These factors may potentially contribute to the increased complications seen in critically ill obese pediatric patients.

Nutrition Assessment and Energy Requirements

Nutrition Assessment

The nutrition screen is designed to identify individuals who are either malnourished or at nutritional risk by assessing characteristics that have been shown to correlate with nutrition problems. Only a very limited number of screens have been validated. Effective nutrition screens are generally quick and reliable, with adequate sensitivity and specificity, and with good positive and negative predicted values [17]. The nutrition assessment is a more comprehensive assessment. It involves interpretation of data to determine if a nutrition problem exists and to what extent. Five distinct areas have been recognized that should be evaluated in the comprehensive assessment; food/nutrition history, biochemical parameters, medical test and procedures, patient history, anthropometric data, as well as a nutrition-focused examination. The nutrition-focused examination helps to evaluate nutrient deficiencies and an estimation of body composition [17]. Once the comprehensive assessment

Table. 17.1 Protein Needs [19]

Protein needs	Age 0–2 years 2–3 g/kg/day
Protein needs	Age 2–13 years 1.5–2 g/kg/day
Protein needs	Age 13–18 years 1.5 g/kg/day

Protein provision requires ongoing reevaluation. Adjust protein provision ↑ or ↓ based on clinical condition, medication and medical therapy

has been completed, the next step is to develop estimated protein and energy goals. Important nutritional goals are to preserve skeletal muscle protein, support wound healing, and the inflammatory response [2, 7].

Energy Requirements in the Critically Ill Child

The basal metabolic rate (BMR) is the energy required to support body temperature, respiratory and cardiac function, and maintain the integrity of the body cells. It is ~65–75% of total energy expenditure (TEE) [1]. TEE is comprised of diet-induced thermogenesis, BMR, and activity [18]. Resting energy expenditure (REE) is 10% above the BMR to account for thermogenesis. Energy needs are acutely altered and variable postinjury and critical illness [19, 20]. To account for the wide range of alterations in energy metabolism during critical illness, measured resting energy expenditure (MREE) is obtained from indirect calorimetry (IC), the most accurate assessment of energy needs [4, 19]. Another method used to obtain MREE is respiratory mass spectrometry [21]. IC is the most frequently used method to obtain MREE. IC determines REE by measuring the volume of oxygen consumed (VO_2) compared to the volume of carbon dioxide produced (CO_2) and does not utilize temperature changes to determine energy needs. IC cannot determine accurate energy measurements in patients with chest tubes in place, endotracheal tube with air leak, extracorporeal membrane oxygenation (ECMO), and high inspired oxygen fraction (FIO_2>0.6) [3]. Indications for IC include children that are underweight, overweight, burns, failure to be weaned or requiring escalation in mechanical ventilation support, neurologic trauma, and hypoxia and/or ischemia. Additional indications for IC include hypometabolic state (hypothyroidism, hypothermia, and pentobarbital coma) or hypermetabolic state (dysautonomic storms, status epilepticus, SIRS) [19].

Numerous studies have used IC to determine MREE in critically ill children. The results have found children of many ages to be hypometabolic during critical illness and postsurgery. Table 17.1 provides a summary of several studies in which MREE was obtained by IC in hospitalized pediatric patients and their age ranges [22–24]. Mehta et al. in a prospective cohort study measuring MREE in critically ill pediatric patients found that in 62% of patients physicians inaccurately assessed their metabolic state, 72% of patients were hypometabolic, and 83% of patients were overfed resulting in excessive cumulative energy (calories). This study further demonstrates that predicated equations are inaccurate, with escalating inaccuracies when stress factors are added to predictive equations to determine energy needs. Children under the age of two are extremely vulnerable to overfeeding [25]. In another study, Briassoulis et al. evaluated the cytokine profile and metabolic patterns (normometabolic, hyper- or hypometabolic based on MREE) of critically ill pediatric patients. During the early phase of illness patients in this study were hypometabolic. Elevated levels of cytokines did not correspond with the hypometabolic state. Only VO_2 and VCO_2 were found to be independently associated with hypometabolism which was associated with an increase in mortality [26]. Both adults and children in some studies have been found to have increased energy expenditure during the early postoperative

Table 17.2 Summary of measured resting energy (MREE) obtained by indirect calorimetry in critically ill pediatric patients. The summary includes the age range, median age, and metabolic status defined as hypometabolic (HYPO), hypermetabolic (HYPER), and normometabolic (NORM)

Research study	Age range	Median age	Researcher's conclusion of metabolic status
Mehta et al. [59]	0. 1–25.8 years	2 years	HYPO, HYPER, & NORM Predominate HYPO
Framson et al [22]	2–17 years	5 years	HYPO
Nydegger et al. [23]	Less than 1 month	16 days	HYPER prior to corrective heart surgery. NORM one week post surgery
Avitzur et al. [24]	3.2–12.3 months	Noncyanotic 12.3 months cyanotic 3.2 months	NORM

Table 17.3 Breakdown of specific energy requirement expressed as kcal/kg/day, needed for basal growth and replacement of excreta losses in neonates 4

Calorie partition in neonates	
Basal metabolic needs	40–70 kcal/kg/day
Growth needs	50–70 kcal/kg/day
Replacement for excreta losses	20 kcal/kg/day
Total	100–120 kcal/kg/day

period while other studies have found no elevation in REE. In children with congenital heart defects, studies using IC have found an increased energy expenditure prior to surgical correction followed by normalization of energy expenditure postcorrective surgery [27]. The optimal energy (calorie) provision following major stress and critical illness is unknown. The most accurate assessments are serial IC measurements due to the variability of MREE during critical illness and the known inaccuracy of predictive equations. Due to the alteration in the hormonal milieu during critically illness and stress, growth does not occur until the convalescent phase of illness [28]. Table 17.2 provides an example of caloric partition in neonates which impacts energy needs during critical illness. Three commonly used predictive equations used to predict REE are given in Table 17.3 for use as a guide when IC is not available or feasible [29, 30]. The impact of stress factors remains unclear and may potentially have more effect in the older child and teenager, more research is needed. The necessity for ongoing revaluation of energy and protein provision in the critically pediatric patient cannot be overemphasized. More research is greatly needed in this area.

Macronutrients, Micronutrients, and Pharmaconutrition

Dietary reference intakes (DRIs) are specific nutrient requirements for age groups and gender for healthy individuals in the United States and Canada [31]. DRIs do not take into account the influence of nutrient requirements in regards to drug–nutrient interactions, toxicity, or disease processes. Therefore, the optimal macronutrients and micronutrients in critical illness are unknown [7]. Macronutrients include protein, carbohydrate (CHO), and fat. Micronutrients consist of vitamins, minerals, and trace elements.

Macronutrients

Protein

Maintenance of protein (nitrogen) equilibrium is the objective in healthy adults who have a protein turnover range of 3.5g/kg/day. Healthy infants and children require a positive nitrogen balance to achieve growth and development; their base line turnover rate is 6g/kg/day [4]. Normal fractional protein synthesis rates in adults is 6-15% and higher in neonates and infants at 15–23% and 15–20% respectively [32]. In critical illness an altered hormonal milieu increases protein breakdown to supply free amino acids for synthesis of enzymes, acute phase reactants, and immunoproteins. This results in a negative protein balance.

This protein breakdown mechanism requires energy. The rate of protein synthesis from the recycling of amino acids during an inflammatory state is doubled that synthesized from dietary protein. Protein turnover in burns and extracorporeal membrane oxygenation (ECMO) is even higher [3]. A significant increase in protein turnover is seen in infants after surgery (25%) and with sepsis there is a 100% elevation of urinary nitrogen excretion [19]. The consequence of significant protein breakdown is evident by inflammation, skeletal muscle wasting, delayed wound healing, and weight loss. Protein breakdown incurred during critical illness does not subside with the provision of exogenous substrate, though the provision of higher protein may help reduce the severity of negative nitrogen balance. Protein stores in adults are nearly doubled that of infants. Therefore, infants and young children are at increased risk for the ill effects of significant protein loss during prolonged injury and/or illness [2]. Additional protein losses can occur in such conditions as the presence of an ileostomy, dialysis, or malnutrition. In these conditions protein needs may be even higher [3, 4, 33]. Medications also affect protein status. For example, glucocorticoid steroids increase proteolysis and postoperative fentanyl decreases protein breakdown in neonates [4, 32]. The addition of intravenous fat into the diet of newborn surgical infants has also been demonstrated to be a protein-sparing mechanism. Protein sparing is the result of lipid being used as an energy source during gluconeogenesis; less protein is then broken down for [2–4]. Therefore, specific protein requirements may be related to age, inflammatory state, and disease state [2, 3, 34]. Children at risk for protein depletion have a greater incidence of multiple system organ dysfunction (MSOD); those with fat store depletion have a greater probability of death in comparison to nutritional healthy children [26].

Nuclear factor kappa B (NF-kβ) activates the release of cytokines during inflammatory states. The activation of cytokines prompts the suppression of insulin receptor signaling leading to insulin resistance, which is seen in both critically ill children and adults [34]. In addition, there appears to be an association between insulin resistance and muscle wasting. A prospective randomized crossover study of critically ill septic adolescents who received parenteral nutrition (PN) containing comparable energy provision and different levels of amino acid support while maintaining tight glycemic control (glucose levels 90–110) found higher amino acid and insulin administration reduced protein breakdown. The researchers concluded that in septic adolescents with insulin resistance, providing 1.5 g/kg/day of protein is inadequate to sustain protein balance in either baseline conditions or during insulin infusion. Supplying protein at 3 g/kg/day demonstrated an impressive tendency towards stimulation of protein synthesis leading to substantial improvement in whole body protein balance even in absence of insulin [34]. The optimal protein provision for the critically ill infant and child are unknown. Current practices have been based on limited studies and data. Table 17.4 outlines clinical guidelines for protein provision for the critically ill infants and child determined by the best available evidence.

Table 17.4 Commonly used predicated equations to estimate resting energy expenditure in children in calories per day [29, 30]

Equations to estimate resting energy in children		
Schofield weight		
Age (years)	Male	Female
<3	(59.512 × W) − 30.4	(61 × W) − 51
3–10	(22.706 × W) + 504.3	(22.5 × W) + 499
10–18	(17.686 × W) + 658.2	(12.2 × W) + 746
World Health Organization *(FAO/WHO/UNU)*		
0–3	(60.9 × W) − 54	(61 × W) − 51
3–10	(22.7 × W) − 495	(22.5 × W) + 499
10–18	(17.5 × W) + 651	(12.2 × W) + 746

W weight(kg), *FAO* The Food and Agriculture Organisation, *WHO* World Health Organization, *UNU* United Nations University

Carbohydrates

Both children and adults during critical illness and injury have an elevated need for glucose, with neonates demonstrating a higher turnover rate of glucose. This is considered to be the result of their increased body surface area and mass to brain ratio. The provision of exogenous glucose in critical illness will not suppress the body's need of heightened glucose production but excess provision increases carbon dioxide synthesis. As a consequence of this heightened glucose demand, protein is readily broken down via gluconeogenesis to produce glucose [3]. Elevated plasma glucose levels are not uncommon due to insulin resistance. Variability in glucose levels and hypoglycemia are accompanied with increased length of hospital stay and mortality [19]. The risk of providing exogenous insulin to achieve tight glucose control is hypoglycemia. Therefore, the decision to use exogenous insulin to achieve tight glucose control should be made after taking into account the individual's risk for hypoglycemia given their age and clinical situation. Various insulin infusion rates and mechanisms of glucose metabolism are being studied to avoid this risk; however, the optimal glucose range to be maintained during critical illness and postsurgery are unknown.

Lipids

Lipids provide a concentrated source of energy and essential fatty acids. During critical illness, sepsis, surgery, and trauma, the turnover of lipids generally occurs at an accelerated rate. Triglycerides release glycerol moiety which can be converted to glucose. Some studies have shown decreased lipid clearance during infections. The consequence of lipid metabolism is lipid peroxidation with formation of free radicals. Proinflammatory cytokines facilitate lipolysis and triglyceride (TG) release, and potentially may impair lipase function and oxidation of fatty acids. Because of this, it is the practice at some facilities to exercise caution when initiating lipids during sepsis/SIRS. Omega-3 fatty acids may also be protective of the lungs during systemic inflammation [35]. A pediatric study examined the impact of sepsis/SIRS on the oxidation of lipids during limited CHO infusion. Respiratory quotient (RQ) levels were comparable to the controls and markers of lipid peroxidation were not altered by the lipid infusion. Even without lipid infusion, TG levels during sepsis/SIRS were significantly higher than the controls [8].

Clinically the respiratory RQ is obtained from IC. The RQ does not detect actual substrate utilization during critical illness, although a RQ>1 has been shown to correlate with overfeeding [36]. Due to limited stores, infants generally are at higher risk for essential fatty acid deficiency. Intravenous fat emulsion comprising omega-3 fatty acids (ω-3 fatty acids) or olive oil is available outside of the United States. The use of these intravenous fat emulsions in some studies demonstrate a reduction in parenteral nutrition-related cholestasis and development of liver disease [4, 10] while others have identified benefit in only a subset of patients [37].

Pharmaconutrition

Pharmaconutrition is the provision of therapeutic doses of nutrients to counteract deficiencies caused by disease or injury in the same manner as pharmacologic agents (Wischmeyer, Heyland). Arginine (ARG), glutamine (GLU), omega fatty acids, various combinations of antioxidants and probiotics are some of the most frequently studied nutrients. A general overview of their specific roles and benefits is provided below [10, 19, 38]. Pharmaconutrients can be classified by function as anti-inflammatory, cell protective, or immune-modulating [38]. More research is needed in the area of pharmaconutrients to further clarify benefits in various pediatric populations by age groups, as well as optimal dosing.

Arginine

Arginine (ARG) is an amino acid that becomes rapidly depleted in significant stressed states such as injury, trauma, or surgery due to increased demand. ARG is a substrate for the vasodilator, nitric oxide. ARG deficiency impairs immune function, especially T-lymphocytes [38]. ARG also has a crucial role in regulation of blood flow, protein synthesis, and repair of tissue and wound injury. Many of the studies outlining benefit in adults have involved immune-enhancing formulas which contain a combination of nutrients such as ARG, omega 3-fatty acids, and nucleotides. The avoidance of ARG supplementation in sepsis stems from the potential for excessive nitric oxide synthesis resulting in an exaggerated SIRS response. The American Society of Parenteral Nutrition (ASPEN), Society for Critical Care Medicine (SCCM), and the European Society for Parenteral and Enteral Nutrition (ESPEN) describe benefits or possible benefit of ARG in adults [38]. The combination of ARG and ω-3 fatty acids after major adult surgeries has shown reduction in infection and length of hospital stay in comparison to standard enteral formulas [38, 39]. In comparison to adults, children's wounds heal more rapidly and completely. Impairment of wound healing in children occurs in critical illness, prematurity, complex wounds, and with comorbidities. Use of negative pressure wound therapy (NPWT) has become increasingly popular in adults, children, and in infants due to decreased sedation needs for dressing changes, provision of a closed clean system, and direct measurement of fluid [40]. In a pediatric study involving six infants, use of an enteral ARG rich supplementation coupled with NPWT was thought to stimulate early healing of infected surgical wounds [41]. NPWT effectiveness and safety in the United States has not been established at this time in neonates, infants, and children [42]. Deficient ARG plasma levels are also found in low birth weight premature infants. ARG supplementation demonstrated improvement in both plasma levels and decreased incidence of necrotizing enterocolitis (NEC) [10, 41]. Further research is needed regarding ARG use in the pediatric population.

Glutamine

Glutamine (GLN) is the most abundant amino acid in plasma and has been studied in both pediatric and adult patients. GLN is a major energy substrate for enterocytes; rapidly proliferating immune cells, lymphocytes, macrophages, and neutrophils. GLN levels decline rapidly in critical illness [10, 35, 38, 43]. GLN plays a significant role in facilitating production of heat shock proteins (HSPs). HSPs are fundamental in cellular recovery following injury. Overall the benefits of reduced infectious complications with GLN supplementation have been found in the severely critically ill adult patient. Supplemental GLN provided parenterally may be more beneficial than enteral supplementation [43]. In a double-blind, randomized, controlled trial of surgical adult patients the investigators concluded that parenteral supplementation of glutamine dipeptide was not only safe but improved glutamine levels and decreased infection rates following cardiac, colonic, and vascular surgery but not pancreatic necrosis surgery [44]. In pediatrics, there is less support for use of GLN supplementation in critical illness. A double blind, randomized controlled trial involving neonates and infants found no change in infection, PICU length of stay, nitrogen balance, or mortality. This study noted no adverse outcomes with the administration of glutamine [45].

Fatty Acids

A pilot study using an adult immune-enhancing enteral formula in 19 critically ill severely burned pediatric patients with acute respiratory distress syndrome (ARDS) found improvement in oxygenation and pulmonary compliance [46]. The formula contained omega 3 fatty acids, eicosapentaenoic acid (EPA), and γ (gamma)-linolenic (GLA). The 2009 A.S.P.E.N guidelines did not recommend the routine use of this formula for critically ill children [19]. Skillman and Wischmeyer endorsed usage in older pediatric patients [10]. More research is needed regarding this potentially promising therapy of immune-enhancing formulas containing anti-inflammatory fatty acids and antioxidants.

Antioxidants

Antioxidants (AOXs) are present in minute amounts and inhibit or delay the oxidation of a substrate. The primary function of AOXs is to counteract oxidative stress which is prevalent in critical illness. AOX levels have been found to be low or depleted in critical illness [47]. AOXs are produced naturally and exogenously provided through food or supplements [48]. The body's natural AOX defense consists of metabolic and nutrient components. The metabolic constituents are synthesized through metabolism and examples include bilirubin, glutathione, L-arginine, and uric acid. The nutrient AOXs cannot be produced endogenously and must be acquired through food or supplement and examples include vitamin A or B-carotene, C, E, selenium, and zinc [48, 49]. In critical illness depleted AOX levels are linked to an increased formation of free radicals, exaggerated systemic inflammatory response, and cell injury leading to increased morbidity and mortality. Heyland et al. reviewed clinical trials involving high-dose AOX supplementation in critically ill patients. They concluded that AOXs have been reported safe and associated with a decrease in mortality in critically ill patients [50]. Potential benefits of AOXs during critical illness are outlined in Table 17.5. Many of the clinical trials involving AOXs have had various vitamin and mineral cocktails involving heterogeneous patients groups. A handful of these trials have been done in children. Pediatric patients with severe burns have been found to have low plasma levels of vitamin D [7, 51]. Additional losses of vitamins and minerals can occur through loss of bodily fluids, such as hemorrhaging and drains [7]. Dylewski et al. found

Table 17.5 Summary of the roles of nutrient antioxidants in critical illness [48, 49]

Antioxidant	Function
Vitamin E	Breaks free radical chains
	Decreases lipid destruction
Vitamin C	Inhabits free radical reactions jointly with vitamin E
Vitamin C and E	Reduces infectious complications post hemorrhagic shock and injury
Selenium	Protects endothelial cells
	Scavenger of free radicals jointly with vitamin E
	Decreases mortality in critical illness and septic shock

plasma and urinary selenium levels to be low in 15 pediatric patients. The researchers concluded that suboptimal selenium status may potentially impact the incidence of infections in pediatric burn patients [52].

Probiotics

Probiotics are nonpathogenic living organisms or food that have the capacity to yield health benefits through modulation of the mucosal milieu in the gastrointestinal tract when consumed in adequate amounts. The use of probiotics in several studies has revealed benefit in both adults and children in infectious diarrhea and clostridium difficile [53]. Probiotic use in premature infants may reduce the incidence of NEC [10]. Higher yield of probiotic benefit may occur with multi-strains vs. mono-strains [54]. However, there are conflicting data regarding probiotic use and safety in critical illness. In a randomized placebo controlled study of probiotics in pediatric intensive care patients, the probiotic group developed more infections than the placebo group although the difference was not statistically significant. As a consequence the study was halted [55]. In a pilot study of 56 critically ill pediatric patients of which 26 of the patients were randomized to receive Lactobacillus Casei Shirota (LCS), no growth of LCS was found in the probiotic group. The researchers concluded LCS did not increase risk of infection [56]. Further studies are warranted to evaluate the efficacy and safety of probiotics in critical illness.

Nutrition Support Barriers, Initiation, and Monitoring

Nutrition Support Barriers

Enteral nutrition (EN) is the preferable routine of nutrition support during critical illness. In adults early initiation of EN within 24–48 h is shown to decrease infectious complications, hospital length of stay, and benefits to the integrity of the intestinal mucosa in comparison to PN. EN is also more cost-effective than PN [57, 58]. Early EN has also been shown to improve nitrogen balance in the critically ill or injured patient. In severe burn patients early EN (24 h) improves nitrogen balance and the provision of caloric intake and a decrease in mortality compared to EN initiated 48 h posthospital admission [57]. Several barriers are repeatedly identified as inhibitors of the provision of EN and attainment of enteral feeding goals in the critically ill patient. Numerous studies and quality control audits measuring enteral nutrition provision compared to medical order and/or established EN goal have led to identification of these barriers. Frequent EN feeding obstacles are listed in Table 17.6

Table 17.6 Common causes for not reaching EN goal volumes [59, 60]

Elevated gastric residual volumes (GRV)
Failure to acquire enteral access or maintain access
Prolonged holding of EN for test and/or procedures
EN held in anticipated of intubation or extubation
Intolerance to EN, diarrhea, emesis
Clogged feeding tube
Fluid regulation

[59, 60]. One of the major obstacles to EN is the measuring of gastric residual volumes (GRV) which lacks efficacy and has undeservingly been used to define tolerance to enteral nutrition. Elevated GRV have been defined as evidence for intolerance of enteral nutrition based on the premise that all gastric contents must empty and gastric residuals indicate delayed gastric emptying with the associated risk of aspiration pneumonia [61]. As a consequence EN is either held or not advanced. The evidence shows little correlation between GRV with EN intolerance or increased risk of aspiration pneumonia. No augmented risk for aspiration pneumonia is associated with an elevated GRV and no decreased risk is associated with a low GRV [62, 63]. Prolonged holding of EN delivery prior and after tests and procedures such as endotracheal intubation and extubation limits delivery. The actual process of obtaining GRV increases the risk of clogging feeding tubes which furthers disrupts EN delivery. When the intact protein in enteral formula mixes with the gastric contents (acidic) the conformation of the protein is altered and coagulation may form leading to a clogged feeding tube, especially in small bore feeding tubes. Medications administered through feeding tubes increase the risk for clogging. The use of liquid medications when feasible can help reduce the risk of tube clogging as can periodic water flushes [64]. Liquid medication may reduce the risk of tube clogging but in turn may increase the risk of diarrhea due to their higher osmotic load [65]. Awaiting the return of bowels sounds is another EN obstacle. Research has demonstrated that the small bowel returns to normal function 4 h postoperatively and early EN is tolerated though bowel sounds are generally absent [61, 66]. Finally, symptoms of diarrhea and emesis are frequent occurrences in the critically ill patient. Measurement and assessment of these occurrences varies extensively, the lack of standardization to define feeding intolerance may in itself be a barrier to delivery of EN. Causes of diarrhea are multifaceted. Frequent known causes of diarrhea are disease state, dysbiosis or dysbacteriosis, antibiotics, and medications in elixir or liquid form promoting an osmotic laxative consequence. Another potential cause is inadequately absorbed fermentable fiber or lack of fiber in the enteral formula [65].

Data have shown that implementation of EN protocols that outline initiation and advancement guidelines for EN increases the delivery and tolerance of EN. Pediatric nutrition support teams increase the utilization of EN while decreasing unwarranted PN use. Protocols regarding enteral tube placement enhance staff expertise in EN tube placement thereby increasing EN delivery [67–69].

Initiation of Nutrition Support

The optimal support method selected for the critically ill and/or the critical surgical patient should be determined by age, clinical condition, underlying disease state, gastrointestinal function, and length of therapy [58]. Numerous decision trees or algorithms have been developed to guide the initiation of nutrition support. In pediatrics there is a dearth of data available to make evidence-based decisions,

Table 17.7 Suggestion for initiation of EN using an isotonic formula preferably. Initiation of EN should be based on medical condition, treatment modalities, and individualized tolerance [58]

Initiation of enteral nutrition (EN)	
Weight < 30–40 kg	Weight > 30–40 kg
Continuous infusion	Continuous infusion
Start 1–2 mL/kg/h	Start at 1 mL/kg/h
Advance to desired goal rate within 24–48 h	Advance to desired goal rate within 24–48 h
Bolus gastric feeding	Bolus gastric feeding
Start at 2.5–5 mL/kg per feed over 5–8 feedings/day gradually advancing to desired goal volume	Start at 2.5–5 mL/kg per feed over 5–8 feedings/day gradually advancing to desired goalvolume

thus clinicians are forced to rely on best practices or data obtained from adult literature. The general premise is that if the gastrointestinal tract is functional EN is utilized and PN is reserved for the nonfunctional GI tract. Gastric is the preferred method for EN delivery while postplyoric is reserved for gastroparesis, gastric outlet obstruction, pancreatitis, and patients with known reflux and aspiration of gastric contents [58]. In hemodynamic instability, EN is frequently withheld due to the requirement for vasoactive medications. Avoidance of EN also occurs during evidence of bowel ischemia [57]. EN is administered by continuous, intermittent, and bolus infusion. The American Society for Enteral and Parenteral Nutrition (A.S.P.E.N.) 2009 suggestions for initiation of EN nutrition can be found in Table 17.7. The recommendations are for initiation of full strength isotonic formula and the avoidance of diluted enteral formula. The diluting of enteral formula increases the probability of microbial contamination leading to diarrhea and EN intolerance. In addition, dilution of enteral formula lowers the formula osmolality. The lower osmolality and higher pH of the diluted formula is more supportive of microbial growth compared to full strength formula [58].

Monitoring of Nutrition Support

Monitoring of biochemical parameters should occur before nutritional support, after initiation of nutrition support, and periodically thereafter. The type of parameters monitored should be based on protocols as well as the patient's underlying illness and disease state. Patients at risk for the refeeding syndrome and metabolic complications should be monitored more closely. Complications of refeeding in malnourished patients can lead to pathophysiological and metabolic complications involving depleted levels of potassium, phosphorus, magnesium, and thiamine leading to cardiac, hepatic, respiratory, and neuromuscular consequences and even death. Depleted biochemical parameters should be corrected prior to the initiation of nutrition support [58]. Electrolyte and glucose management involves monitoring many parameters as a result of fluid shifts, renal function, bodily secretions, and increased insensible losses and may need to be reviewed on a daily basis depending on clinical condition. Abnormal phosphate, magnesium, and acid–base imbalances frequently occur during critical illness particularly in those with sepsis, SIRS, and preexisting deficiencies. In stress states there is hepatic reprioritization of protein synthesis. Protein levels are inversely related to the C-reactive protein (CPR) level. When the CRP is elevated, protein synthesis of albumin and prealbumin is decreased compared to when the CRP is less than 2. Albumin levels are also skewed independent of nutrition status by fluid status, intravenous albumin provision, trauma, sepsis, and liver disease. This is not a reliable monitor of nutrition status during these states and critical illness [2, 3, 7].

Summary and Future Research

Critically ill children like adults experience the metabolic response to stress which varies by age. Children, especially young children, due to their low protein reserves are particularly vulnerable in prolonged stress to the detrimental effects of the altered hormonal milieu. The role of nutrition support is to help preserve skeletal muscle and support organ and immune function. The optimal provision of macronutrients, micronutrients, energy, and nutrition support in critically ill children is unknown. It is well established that predictive equations inadequately predict energy needs during critical illness and indirect calorimetry is more accurate. Research in the area of nutrition support for the critically ill child is urgently needed.

References

1. McHoney M, Eaton S, Pierro A. Metabolic response to surgery in infants and children. Eur J Pediatr Surg. 2009;19(5):275–85.
2. Mehta N, Jaksic T. The critically Ill child. In: Duggan C, Watkins JB, Walker WA, editors. Nutrition in pediatrics: basic science, clinical applications. 4th ed. Hamiliton, Ontario: Decker, B.C; 2008. p. 663–73.
3. Mehta N, Jaksic T. Nutrition support of the pediatric patient. In: Holcomb GI, Murphy JP, editors. Ashcraft's pediatric surgery. 5th ed. Philadelphia, PA: Saunders, P.A; 2010. p. 19–31.
4. Pierro A, Eaton S. Metabolism and nutrition in the surgical neonate. Semin Pediatr Surg. 2008;17(4):276–84.
5. Bulger EM, Maier RV. Antioxidants in critical illness. Arch Surg. 2001;136(10):1201–7.
6. Matfin G, Akueniz J, Guven S. Diabetes mellitus and the metabolic syndrome. In: Porth CM, editor. Essentials of pathophysiology, concepts of altered health stages. 2nd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2007. p. 699–723.
7. Mehta NM, Duggan CP. Nutritional deficiencies during critical illness. Pediatr Clin North Am. 2009;56(5): 1143–60.
8. Caresta E, Pierro A, Chowdhury M, Peters MJ, Piastra M, Eaton S. Oxidation of intravenous lipid in infants and children with systemic inflammatory response syndrome and sepsis. Pediatr Res. 2007;61(2):228–32.
9. Cruccetti A, Pierro A, Uronen H, Klein N. Surgical infants on total parenteral nutrition have impaired cytokine responses to microbial challenge. J Pediatr Surg. 2003;38(1):138–42. discussion 138–42.
10. Skillman HE, Wischmeyer PE. Nutrition therapy in critically ill infants and children. JPEN J Parenter Enteral Nutr. 2008;32(5):520–34.
11. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. N Engl J Med. 2007;357(11):1121–35.
12. Jeschke MG, Gauglitz GG, Kulp GA, et al. Long-term persistance of the pathophysiologic response to severe burn injury. PLoS One. 2011;6(7):e21245.
13. Chung DH, Herndon DN. Burns. In: Holcomb GI, Murphy JP, editors. Ashcraft's pediatric surgery. 5th ed. Philadelphia, PA: Saunders, P.A; 2010. p. 154–66.
14. Jeschke MG, Kulp GA, Kraft R, et al. Intensive insulin therapy in severely burned pediatric patients: a prospective randomized trial. Am J Respir Crit Care Med. 2010;182(3):351–9.
15. Bailey KA. Special considerations in the critically ill morbidly obese child. Crit Care Clin. 2010;26(4):699–702.
16. Torres-Leal FL, Fonseca-Alaniz MH, Rogero MM, Tirapegui J. The role of inflamed adipose tissue in the insulin resistance. Cell Biochem Funct. 2010;28(8):623–31.
17. Charney P, Marian M. Nutrition screening and nutrition assessment. In: Charney P, Malone AM, Faulhaber D, editors. ADA Pocket guide to nutrition assessment. 2nd ed. Chicago, IL: American Dietetic Association; 2009. p. 1–19.
18. Haugen HA, Chan LN, Li F. Indirect calorimetry: a practical guide for clinicians. Nutr Clin Pract. 2007;22(4):377–88.
19. Mehta NM, Compher C, A.S.P.E.N. Board of Directors. A.S.P.E.N. Clinical Guidelines: nutrition support of the critically ill child. JPEN J Parenter Enteral Nutr. 2009;33(3):260–76.
20. Havalad S, Quaid MA, Sapiega V. Energy expenditure in children with severe head injury: lack of agreement between measured and estimated energy expenditure. Nutr Clin Pract. 2006;21(2):175–81.
21. Li J, Zhang G, Herridge J, et al. Energy expenditure and caloric and protein intake in infants following the Norwood procedure. Pediatr Crit Care Med. 2008;9(1):55–61.
22. Framson CM, LeLeiko NS, Dallal GE, Roubenoff R, Snelling LK, Dwyer JT. Energy expenditure in critically ill children. Pediatr Crit Care Med. 2007;8(3):264–7.

23. Nydegger A, Walsh A, Penny DJ, Henning R, Bines JE. Changes in resting energy expenditure in children with congenital heart disease. Eur J Clin Nutr. 2009;63(3):392–7.
24. Avitzur Y, Singer P, Dagan O, et al. Resting energy expenditure in children with cyanotic and noncyanotic congenital heart disease before and after open heart surgery. JPEN J Parenter Enteral Nutr. 2003;27(1):47–51.
25. Mehta NM, Bechard LJ, Dolan M, Ariagno K, Jiang H, Duggan C. Energy imbalance and the risk of overfeeding in critically ill children. Pediatr Crit Care Med. 2011;12(4):398–405.
26. Briassoulis G, Venkataraman S, Thompson A. Cytokines and metabolic patterns in pediatric patients with critical illness. Clin Dev Immunol. 2010;2010:354047.
27. Herman R, Btaiche I, Teitelbaum DH. Nutrition support in the pediatric surgical patient. Surg Clin North Am. 2011;91(3):511–41.
28. Jaksic T, Shew SB, Keshen TH, Dzakovic A, Jahoor F. Do critically ill surgical neonates have increased energy expenditure? J Pediatr Surg. 2001;36(1):63–7.
29. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr. 1985;39 Suppl 1:5–41.
30. Energy and Protein Requirements. Report of a joint FAO/WHO/UNU expert consultation. World Health Organ Tech Rep Ser. 1985;724:1–206.
31. American Dietetic Association. Position of the American Dietetic Association: use of nutritive and nonnutritive sweeteners. J Am Diet Assoc. 2004;104(2):255–75.
32. Verbruggen SC, Schierbeek H, Coss-Bu J, Joosten KF, Castillo L, van Goudoever JB. Albumin synthesis rates in post-surgical infants and septic adolescents; influence of amino acids, energy, and insulin. Clin Nutr. 2011;30(4):469–77.
33. Maursetter L, Kight CE, Mennig J, Hofmann RM. Review of the mechanism and nutrition recommendations for patients undergoing continuous renal replacement therapy. Nutr Clin Pract. 2011;26(4):382–90.
34. Verbruggen SC, Coss-Bu J, Wu M, et al. Current recommended parenteral protein intakes do not support protein synthesis in critically ill septic, insulin-resistant adolescents with tight glucose control. Crit Care Med. 2011;39(11):2518–25.
35. Cook RC, Blinman TA. Nutritional support of the pediatric trauma patient. Semin Pediatr Surg. 2010;19(4):242–51.
36. McClave SA, Lowen CC, Kleber MJ, McConnell JW, Jung LY, Goldsmith LJ. Clinical use of the respiratory quotient obtained from indirect calorimetry. JPEN J Parenter Enteral Nutr. 2003;27(1):21–6.
37. Nasr A, Diamond IR, de Silva NT, Wales PW. Is the use of parenteral omega-3 lipid emulsions justified in surgical neonates with mild parenteral nutrition-associated liver dysfunction? J Pediatr Surg. 2010;45(5):980–6.
38. Wischmeyer P. Nutritional pharmacology in surgery and critical care: 'you must unlearn what you have learned'. Curr Opin Anaesthesiol. 2011;24(4):381–8.
39. Drover JW, Cahill NE, Kutsogiannis J, et al. Nutrition therapy for the critically ill surgical patient: we need to do better! JPEN J Parenter Enteral Nutr. 2010;34(6):644–52.
40. Contractor D, Amling J, Brandoli C, Tosi LL. Negative pressure wound therapy with reticulated open cell foam in children: an overview. J Orthop Trauma. 2008;22(10 Suppl):S167–76.
41. Masumoto K, Nagata K, Oka Y, et al. Successful treatment of an infected wound in infants by a combination of negative pressure wound therapy and arginine supplementation. Nutrition. 2011;27(11–12):1141–5.
42. Negative Pressure Wound Therapy. http://www.fda.govSafety/MedWatch/SafetyAlertsforHumanMedical. Accessed 08 Aug 2011.
43. Vanek VW, Matarese LE, Robinson M, et al. A.s.p.e.N. Position paper: parenteral nutrition glutamine supplementation. Nutr Clin Pract. 2011;26(4):479–94.
44. Estivariz CF, Griffith DP, Luo M, et al. Efficacy of parenteral nutrition supplemented with glutamine dipeptide to decrease hospital infections in critically ill surgical patients. JPEN J Parenter Enteral Nutr. 2008;32(4):389–402.
45. Albers MJ, Steyerberg EW, Hazebroek FW, et al. Glutamine supplementation of parenteral nutrition does not improve intestinal permeability, nitrogen balance, or outcome in newborns and infants undergoing digestive-tract surgery: results from a double-blind, randomized, controlled trial. Ann Surg. 2005;241(4):599–606.
46. Mayes T, Gottschlich MM, Kagan RJ. An evaluation of the safety and efficacy of an anti-inflammatory, pulmonary enteral formula in the treatment of pediatric burn patients with respiratory failure. J Burn Care Res. 2008;29(1):82–8.
47. Berger MM. Antioxidant micronutrients in major trauma and burns: evidence and practice. Nutr Clin Pract. 2006;21(5):438–49.
48. Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. Int J Biomed Sci. 2008;4(2):89–96.
49. Collier BR, Giladi A, Dossett LA, Dyer L, Fleming SB, Cotton BA. Impact of high-dose antioxidants on outcomes in acutely injured patients. JPEN J Parenter Enteral Nutr. 2008;32(4):384–8.
50. Heyland DK, Dhaliwal R, Suchner U, Berger MM. Antioxidant nutrients: a systematic review of trace elements and vitamins in the critically ill patient. Intensive Care Med. 2005;31(3):327–37.

51. Gottschlich MM, Mayes T, Khoury J, Warden GD. Hypovitaminosis D in acutely injured pediatric burn patients. J Am Diet Assoc. 2004;104(6):931–41. Quiz 1031.
52. Dylewski ML, Bender JC, Smith AM, et al. The selenium status of pediatric patients with burn injuries. J Trauma. 2010;69(3):584–8. discussion 588.
53. Rohde CL, Bartolini V, Jones N. The use of probiotics in the prevention and treatment of antibiotic-associated diarrhea with special interest in Clostridium difficile-associated diarrhea. Nutr Clin Pract. 2009;24(1):33–40.
54. Deshpande GC, Rao SC, Keil AD, Patole SK. Evidence-based guidelines for use of probiotics in preterm neonates. BMC Med. 2011;9:92.
55. Honeycutt TC, El Khashab M, Wardrop 3rd RM, et al. Probiotic administration and the incidence of nosocomial infection in pediatric intensive care: a randomized placebo-controlled trial. Pediatr Crit Care Med. 2007;8(5):452–8. Quiz 464.
56. Srinivasan R, Meyer R, Padmanabhan R, Britto J. Clinical safety of Lactobacillus casei shirota as a probiotic in critically ill children. J Pediatr Gastroenterol Nutr. 2006;42(2):171–3.
57. Mehta NM. Approach to enteral feeding in the PICU. Nutr Clin Pract. 2009;24(3):377–87.
58. Bankhead R, Boullata J, Brantley S, et al. Enteral nutrition practice recommendations. JPEN J Parenter Enteral Nutr. 2009;33(2):122–67.
59. Mehta NM, McAleer D, Hamilton S, et al. Challenges to optimal enteral nutrition in a multidisciplinary pediatric intensive care unit. JPEN J Parenter Enteral Nutr. 2010;34(1):38–45.
60. Rogers EJ, Gilbertson HR, Heine RG, Henning R. Barriers to adequate nutrition in critically ill children. Nutrition. 2003;19(10):865–8.
61. Warren J, Bhalla V, Cresci G. Postoperative diet advancement: surgical dogma vs. evidence-based medicine. Nutr Clin Pract. 2011;26(2):115–25.
62. DeLegge MH. Managing gastric residual volumes in the critically ill patient: an update. Curr Opin Clin Nutr Metab Care. 2011;14(2):193–6.
63. Hurt RT, McClave SA. Gastric residual volumes in critical illness: what do they really mean? Crit Care Clin. 2010;26(3):481–90. Viii–ix.
64. Lord LM. Restoring and maintaining patency of enteral feeding tubes. Nutr Clin Pract. 2003;18(5):422–6.
65. Whelan K, Schneider SM. Mechanisms, prevention, and management of diarrhea in enteral nutrition. Curr Opin Gastroenterol. 2011;27(2):152–9.
66. Franklin GA, McClave SA, Hurt RT, et al. Physician-delivered malnutrition: why do patients receive nothing by mouth or a clear liquid diet in a university hospital setting? JPEN J Parenter Enteral Nutr. 2011;35(3):337–42.
67. Meyer R, Harrison S, Sargent S, Ramnarayan P, Habibi P, Labadarios D. The impact of enteral feeding protocols on nutritional support in critically ill children. J Hum Nutr Diet. 2009;22(5):428–36.
68. Lambe C, Hubert P, Jouvet P, Cosnes J, Colomb V. A nutritional support team in the pediatric intensive care unit: changes and factors impeding appropriate nutrition. Clin Nutr. 2007;26(3):355–63.
69. Gurgueira GL, Leite HP, Taddei JA, de Carvalho WB. Outcomes in a pediatric intensive care unit before and after the implementation of a nutrition support team. JPEN J Parenter Enteral Nutr. 2005;29(3):176–85.

Part II
GI Tract Considerations

Chapter 18
Parenteral Nutrition in Infants and Children

Consuelo Pedrón-Giner, Cecilia Martínez-Costa, and José Manuel Moreno Villares

Keypoints

- Parenteral nutrition is an artificial support modality that provides the human organism with fluids, energy, and nutrients. These are directly administered to the venous network.
- Parenteral nutrition is recommended in cases where the patient's nutritional needs cannot be fully satisfied through enteral means.
- Parenteral nutrition must be applied for the shortest period of time possible because it uses a non-physiological path, lacks a trophic effect on the intestinal mucosa, can produce numerous and serious complications, and entails a higher cost than enteral nutrition.
- The selection of the most appropriate venous access (peripheral or central) and catheter type depends on the patient's conditions. A central venous catheter is necessary for total parenteral nutrition.
- Nutrient supply must be balanced and adjusted according to the patient's age, nutritional status, and underlying disease.
- The complications of parenteral nutrition can be minimized with strict clinical, analytical, and technical surveillance.

Keywords Pediatric parenteral nutrition • Nutritional support • Central venous catheter • Monitoring • Parenteral nutrition-associated liver disease • Complications

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Abbreviations

AN	Artificial nutrition
CVC	Central venous catheter
EFA	Essential fatty acids
EN	Enteral nutrition
ICV	Inferior caval vein
PN	Parenteral nutrition
PNALD	PN-associated liver disease
REE	Resting energy expenditure
SCV	Superior caval vein

Introduction

Parenteral nutrition (PN) is the technique of artificial nutrition (AN) that provides the human organism with fluids, energy, and nutrients, which go directly to the circulatory system through the venous network. The main aim of AN is to recover or maintain the nutritional status, enhancing the optimal growing and development of the child. Additionally, in some cases AN enables to control the underlying disease of the patient [1, 2].

Opposite to enteral nutrition (EN), that passes nutrients through the digestive tract, PN is much more complex: it uses a nonphysiological path in which the response to nutritional input is different to the one obtained by EN, and with no trophic effect on intestinal mucosa; derived complications are more numerous and serious and, lastly, it entails a much higher cost. Therefore, PN is not the primary option of AN [3]. Nevertheless, EN and PN are not excluding techniques, and their combined usage is presently becoming more frequent, enabling to reduce the duration and quantity of intravenous infusions, even in the most serious cases.

Characteristically, a child's organism is in continuous change from birth to adolescence. During child development size increases and body composition changes, causing the nutritional needs to be proportionally greater to those of the adult. Immaturity implies special requirements both in type and quality of the nutrients. The disease worsens these physiological conditions. Furthermore, children depend upon adults; they are part of a family that must be involved in the treatment and thereby in the nutritional support.

The outcome of this compilation of variables is that the child is particularly vulnerable to the lack of nutrients. This is the reason for which nutritional treatment must be started early and adapted to the biological circumstances of each specific age. These facts further increase the complexity of the PN technique in childhood, so they should be carried out by specialized support teams [4].

Indications

PN is recommended in cases when the patient's nutritional needs cannot be fully satisfied through enteral means, both in already undernourished children and in those in risk of undernourishment because of digestive diseases or of other acute or chronic diseases [2, 5, 6] (Table 18.1). The commonly accepted criteria for nutritional intervention are not based on evidence and have been recently

Table 18.1 Indications for parenteral nutrition

Primary gastrointestinal diseases
Gastrointestinal surgery:
Small bowel resection
Mid-gut volvulus
Other intestinal or abdominal wall malformations
Transplantations
Malabsorption:
Short small bowel
Intractable diarrhea
Severe inflammatory bowel disease
Gastrointestinal fistulas
Others:
Necrotizing enterocolitis
Dysmotility syndromes (primary or not)
Severe acute pancreatitis
Chemotherapy or radiation therapy induced mucositis
Uncontrollable vomiting
Primary extraintestinal diseases
Low-birth weight infants
Catabolic or hypermetabolic states:
Burns
Malignancies
Marrow and organ transplantation
Sepsis
Polytrauma
Other: cardiac or respiratory diseases
Organ failures:
Acute hepatic failure
Acute renal failure
Multiorgan failure
Inborn errors of metabolism

summarized by the ESPGHAN's Nutritional Committee [7]. Regarding infants and children, PN would be recommended when:

- Strict fasting is expected for a period of at least 3 days in children under 1 year or 5 days in children over that age [8, 9].
- When achieving over 60–80 % of energetic requirements is not possible by enteral means for more than 10 days, or even before when the patient is already undernourished.

PN must be applied for the shortest period possible. In order to ensure 2/3 of the estimated requirements as soon as possible and hence discontinue parenteral nutrition, the promotion of oral nutrient intake (or, if this is not possible, enteral nutrition support) is essential.

Venous Access

The venous access selection (peripheral or central) and the catheter type will depend upon the following variables: estimated treatment duration and the patient's characteristics including nutritional requirements, nutritional status, underlying disease, and available vascular accesses [6].

Peripheral venous accesses are located in subcutaneous veins, of easy placement. These are of short duration and permit only the infusion of solutions of limited osmolarity (600–800 mOsm) to prevent infusion extravasations and phlebitis. These are employed in cases where PN adds up to enteral inputs, and when central venous accesses cannot be managed.

Central venous accesses permit the input of volumes and solutions with high caloric density and osmolarity, and are essential to accomplish complete PN [5]. These are placed by inserting the catheter through the subclavian vein, internal jugular vein, or femoral vein or through the peripheral veins. The catheter edge must remain correctly settled and always confirmed radiologically [10]: in the superior caval vein (SCV) where it meets the cardiac atrium when the access drains to the SCV, or over the renal veins in the case of the inferior caval vein (ICV). In newborn, the umbilical vein can be exceptionally used, always for the shortest possible time and located in the ICV.

The insertion of central venous catheter (CVC) can be implemented in percutaneous form, blindly or guided through fluoroscopy or preferably with aid of ecography [11], and by chirurgical dissection. There are several types of CVC: peripherally inserted central (PIC) line, percutaneous insertion catheters, and long-duration catheters, for patients in which it is estimated longer duration than 3–6 weeks, or in cases of home PN. Long-duration catheters can be tunneled (Hickman®, Broviac® type) or introduced as implantable ports. The CVC's diameter must be the smallest possible to minimize the risks of vascular damage and may have one or several lights.

Care needed for the CVCs is linked with the appearance of related complications, so this care must be strengthened and protocolized [12] by each institution. Implementation will be made through aseptic techniques, the antiseptic hand hygiene (even when sterile gloves are used), skin and connection device disinfection, and permeability supervision are all obligatory before any manipulation.

Nutrient Requirements

Energy

Energy needs vary depending on the patient's age, nutritional status, physical activity, and diseases [5, 6]. Except in cases where indirect calorimetry is available, resting expenditure energy (REE) calculations will be made through predictive equations, function of the child's individual characteristics, [13–17] (Table 18.2). A factor depending on activity and stress will be applied to this REE, which will generally not be very high to prevent the consequences of overnutrition.

It is important to consider that most patients receiving PN are frequently admitted to the hospital for variable periods of time, and therefore are subjected to different degrees of metabolic stress. In infants the maximum recommended input is 90–100 kcal/kg/day.

Energy input must be calculated precisely without disturbing the equilibrium between the distinct macronutrients: 150–200 nonprotein kcal are recommended per gram of nitrogen.

Proteins

Protein input is made in L-aminoacid form. In children, especially in infants, proteins solutions must have a specific composition, adapted to the needs and enzymatic systems' immaturity. No agreement has yet been reached over the age limit for their usage [6]. Recommendations are 2.3–2.7 (1.5–3) g/kg/day in the newborn; 2.0–2.5 (1.0–2.5) for children between 2 months and 3 years of age; 1.5–2.0 (1.0–2.0) between years 3–5; 1.0–1.5 (1.0–2.0) from age 6 to adolescence [5, 10, 16]. In every case, these must suppose about 12–16 % of the total energetic input.

Table 18.2 Equations for calculating basal metabolic rate (BMR) or resting energy expenditure (REE) and energy requirements in PN (kcal/day)

	Schofield (BMR)		WHO
Calculation	Using weight	Using weight and height	(REE)
Male:			
0–3 years[1]	59.48 × Wt − 30.33	0.167 × Wt + 1517.4 × Ht − 617.6	60.9 × Wt − 54
3–10 years	22.7 × Wt + 505	19.6 × Wt + 130.3 × Ht + 414.9	22.7 × Wt + 495
10–18 years	13.4 × Wt + 693	16.25 × Wt + 137.2 × Ht + 515.5	17.5 × Wt + 651
Female:			
0–3 years[1]	58.29 × Wt − 31.05	16.25 × Wt + 1023.2 × Ht − 413.5	61 × Wt − 51
3–10 years	20.3 × Wt + 486	16.97 × Wt + 161.8 × Ht + 37.2	22.4 × Wt + 499
10–18 years	17.7 × Wt + 659	8.365 × Wt + 465 × Ht + 200	12.2 × Wt + 746

Daily energy needs (kcal/day): BMR or REE × constant (1.1–1.2)

Special considerations:

[1]**Infants <9 kg weight** (16):

-Total energy needs (kcal/day):

Using weight: [98.07 × Wt (kg)] − 121.73

Using weight and height: [10.66 × Ht (cm)] + [73.32 × Wt (kg)] − 635.08

-REE (kcal):

Using weight: [84.5 × Wt (kg)] − 117.33

Using weight and height: [10.12 × Ht (cm)] + [61.02 × Wt (kg)] − 605.08

Intensive Care Unit (5):

-Energy Expenditure (Kcal/day): [(17 × age in months) + (48 × weight in kg) + (292 × body temperature in °C) − 9,677] × 0.239.

Obese adolescens (15, 17):

Male: [16.6 × Wt (kg)] + [77 × Ht (m)] + 572

Female: [7.4 × Wt (kg)] + [482 × Ht (m)] + 217

Wt = weight (kg); *Ht* = length (m)

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Lipids

Lipids solutions must be included in PN because they contain essential fatty acids (EFA) and since of their high caloric concentration that enables to diminish the solutions' osmolarity and the negative effects of glucose overdose. An amount between 25 % and 40 % of nonprotein calories is recommended. In infants, the maximum quantities will be 3–4 g/kg/day (0.13–0.17 g/kg/h) and 2–3 g/kg/day (0.08–0.13 g/kg/h) in the rest of cases [5, 16]. In specific cases (severe infections, neonatal hyperbilirubinemia, thrombocytopenia, liver and lung diseases) its usage must be carefully considered, guaranteeing the EFA input (0.5–1 g/kg/day) and monitoring triglycerides levels (ideally <150 mg/dL).

Since they produce less rising of plasmatic lipids, 20 % solutions will be employed. There are several types of solutions, depending on the fat employed (soya, coconut, olive, and fish oil) and their percentage of the mix [18]. Presently, emulsions made exclusively with soya oil are not recommended [19]. Administration of the mix can be done in conjunction with amino acids and glucose as ternary solutions, once the solution's stability has been revised, or independently in any other case [6].

Carbohydrates

D-Glucose is the only carbohydrate indicated in PN pediatrics. A dose between 60 % and 75 % of nonprotein calories is recommended. The infusion rhythm must be progressive and consider the patient's age. Maximum oxidation capacity, which diminishes considerably in critical sick patients,

must never be surpassed [5, 20]. Excessive glucose influences important secondary effects: hyperglycemia, liver fat deposits and cholestatic jaundice, and increase in CO_2 production, and infectious complications. Addition of insulin is indicated in cases of hyperglycemia with no easy control.

Fluid and Electrolytes

Liquid requirements change with age, weight, hydration state, certain environmental factors (radiant heat, phototherapy, etc.), and the patient's sickness.

In newborn, inputs will be realized carefully and depending on the phase of postnatal adaption [5, 6]: right after birth (until the maximum weight loss is reached, 3–6 days), intermediate (5–15 days), and of stable growth. Inputs of 60–120, 140, and 140–170 mL/kg/day, respectively, will be administered. After the first month and until 12 months of age, liquid volume will be 100 mL/kg/day, and inputs will be calculated according to the Holliday–Segar method for calculating maintenance fluid requirements (100 mL/kg/day for the first 10 kg, with an additional 50 mL/kg/day for every kg between 11–20 kg and 20 mL/kg/day for every kg above 20 kg). In both cases, extraordinary losses depending on presence of vomit, diarrhea, fever, etc. will be considered, together with those circumstances in which fluid input restriction is required because of renal insufficiency or edema presence, among others [5, 6, 20].

Electrolyte input will be made after the second day of life. Postnatal adaptation changes will be adjusted in newborn. In children over one month, 2–3 mEq/kg/day of sodium and chloride and 1–3 mEq/kg/day of potassium will be administered.

It is indispensable to consider liquid and electrolyte inputs received by the patients through pharmacotherapy and other perfusions. In case of ostomy, special care will be given to reposition (independently of PN volume) through solutions that consider the lost intestinal continent.

In undernourished patients, inputs will be made slowly to prevent overfeeding syndrome.

Minerals and Oligoelements

Mineral and trace elements requirements vary depending on age and weight [5, 6, 10, 16, 20] (Table 18.3). Total calcium and phosphorus quantities are limited by their solubility and the proportion between both substances. The usage of organic sources of phosphate (sodium glycerophosphate) helps to avoid this problem. Its administration to children is completely safe. The recommended dose to obtain the best retention capacity is a molar calcium/phosphorus relation of 1.1–1.3/1 or a weigh relation of 1.3–1.7/1.

There are oligoelement solutions designed specifically for pediatric patients, but where individual adjustments are not possible. Only exclusive formulations of Zn are available, mainly indicated in cases of diarrhea or excessive stoma output. Manganese excess must be prevented in the long-term PN.

Vitamins

Optimal vitamin requirements for their use in PN are not well established, although there are formulations that follow present recommendations [5, 6, 10, 16, 20] (Table 18.4). These vitamins may be inactivated by the light, or adhere to the containers or infusion systems, so levels must be constantly monitored to make adjustments.

Table 18.3 Recommended intakes for parenteral supply of minerals and trace elements

Minerals	TN/kg/day	<1 year/kg/day	1–11 years /kg/day	12–15 years/kg/day
Calcium (mg)	40–60	20–25	10–20	4.5–9
(mMol)	1–1.5	0.5–0.6	0.25–0.5	0.12–0.2
(mEq)	2–3	1–1.2	0.5–1	0.2–0.4
Phosphorus (mg)	30–45	10–30	8–22	5–10
(mMol)	1–1.5	0.3–1	0.25–0.7	0.16–0.3
(mEq)	2–3	0.6–2	0.5–1.5	0.3–0.6
Magnesium (mg)	3–6	3–6	3–6	2.5–4.5
(mMol)	0.12–0.25	0.12–0.25	0.12–0.25	0.1–0.2
(mEq)	0.25–0.5	0.25–0.5	0.25–0.5	0.2–0.4

Trace elements	TN—1 year mcg/kg/day	Other ages mcg/kg/day
Fe	100	1 mg/day
Zn	250 < 3month 100 > 3month	50 (max 5,000 mcg/day)
Cu	20	20 (max 300 mcg/day)
Se	2	2 (max 30 mcg/day)
Cr	0.2	0.2 (max 5 mcg/day)
Mn	1	1 (max 50 mcg/day)
Mo	0.25	0.25 (max 5 mcg/d)
I	1	1 (max 50 mcg/d)

TN Term newborn; *Max* maximum
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Table 18.4 Recommended intakes for parenteral supply of vitamins. Vitamin preparations

Vitamin	Infant-children (dose/day)	Soluvit® N + Vitalipid N Infant® 3,8 + 10 mL	Soluvit® N + Vitalipid N Infant® 10 + 10 mL	Infuvite Pediatric® 5 mL
Vitamin A (UI)	1,500–2,300	2,300	2,300	2,300
Vitamin E (mg)	7–10	6.4	6.4	7
Vitamin K (mcg)	50–200	200	200	200
Vitamin D (UI)	400	400	400	400
Ascorbic acid (mg)	80–100	37.7	100	80
Thiamine (mg)	1.2	0.94	2.5	1.2
Riboflavin (mg)	1.4	1.35	3.6	1.4
Pyridoxine (mg)	1	1.5	4	1
Niacin (mg)	17	15.08	40	17
Pantothenic acid (mg)	5	5.65	15	5
Biotin (mcg)	20	22.62	60	20
Folic acid (mcg)	140	150.8	400	140
B_{12}Vitamin (mcg)	1	1.88	5	1

Soluvit® N (water soluble vitamins), the vial was reconstituted in 10 mL; Vitalipid N Infant® (fat soluble vitamins) vial 10 mL
Infuvite Pediatric®: vial 1 mL (folic acid, biotin, B_{12} vitamin) and vial 4 mL (other vitamins). Dose Term newborn <3 kg: 3 mL; Other: 5 mL
Equivalence: Vitamin A 1 mcg = 3.3 UI; Vitamin D 1 mcg = 10 UI
Modified from [6]. Reprinted with permission from Nutrición Hospitalaria

PN Organization and Administration

Ordering and Preparation

The prescription of PN is a considerably complex process [6]. To prevent errors, recommendations include clarified protocols, well-designed printed application forms and, if possible, in electronic form [21]. The PN efficiency can be enhanced with the use of standardized solutions (traditionally of little use in pediatrics). Prescription must be made daily in any case [5].

Parenteral preparation is carried out by the pharmacy services in horizontal laminar flow chambers, following detailed instruction guides relating to the products in use, the order of inputs in the mix, and its future storage and protection. All bags must be correctly identified with the patient's name and its composition. PN "all-in-one" solutions ask for less manipulation and material and personal needs, an option when the emulsion's stability enables its use [22]. Diary vitamin and oligoelement doses are recommended in the same bag.

Administration

Material [5, 6]

Multilayered bags should be used to store the nutritional solution in a dark refrigerator. Both the bag and the system of administration during infusion should be protected from the light to avoid oxidation and prevent its oxidation effects on the mix. Infusion will be made through volumetric pumps. Three-to-one preparation and 1.2-μm filters should be used. In binary mixes, 0.22-μm filters are recommended.

Modes of Administration/Delivery

The therapeutic nutritional aim should be reached in 2–3 days, if the fluid administration is correct throughout the entire process. The increases will be slower (5–7 days) when the patients are undernourished, to prevent the re-feeding syndrome [15]. PN infusion will be commonly made in continuous form, or exceptionally in shorter time periods (cyclic PN) in patients with hepatic diseases, and in long duration or domiciliary PN. Interruption of PN will be made as soon as possible, once nutrient input by digestive means is secured.

Monitoring

The first stage of PN monitoring is a thorough assessment prior to the start of the nutritional support, where indications, nutritional status, venous access, and therapeutic aims are specified [3, 5]. Then, periodic assessments will be made to evaluate aspects related with [8, 15]:

- Administration: diary volume of PN and other, technique and use of materials, venous access care, medicament administration.
- Tolerance, both clinic and biochemical, complication detection and solving, intercurrent diseases.
- Efficiency, through anthropometric means and biochemical parameters.

Clinic controls must include the diary hydric balance, assessing the PN administered volume, physical assessment, and body parameters. Weight will be assessed daily; other anthropometric parameters (weight, height, and cranial circumference) will be recorded monthly. Biochemical controls will be made individually, and include hemograms with differential counting, electrolytes, urea/creatinine, glucose, acid/base status, calcium/phosphorus, albumin, hepatic enzymes and bilirubin, cholesterol, and triglycerides. Glucose, electrolytes parameters, and cetonic bodies will be assessed in urine. Vitamin, oligoelement, and osseous mineralization will be assessed in patients with long-term PN.

Complications

CVC-related complications

- Vascular insertion may cause several complications, including pneumothorax, laceration of a vessel, cardiac perforation, cardiac tamponade, etc. These complications are substantially reduced when imaging techniques are used during placement [11]. Accidental breakings or displacements accompanied of venous access loss or vascular perforation are frequent in infancy, so CVC must be fixed correctly.
- Thrombotic and nonthrombotic occlusion of the catheter should be suspected when drainage occurs around the catheter or when the alarm is set off by infusion pump pressure. Occlusion may be a consequence of either external compression, having the distal extreme pushing the vascular wall, or light obstruction because of lipid or drugs deposits, blood or fibrin. Successful results have been obtained with alcohol, chlorhydric acid, and other substances in case of lipid or drug deposits [23], and with fibrinolytic treatment (alteplase [24]) in case of blood or fibrin occlusion. Catheter flushing with saline solutions, after medicament administration or extractions [25] is recommended to prevent occlusion.
- Venous thrombosis, frequent in long duration CVC, may be asymptomatic or cause severe pain, and local or diffuse edema (thromboembolism). To prevent this, the catheter must be fixed correctly and free of possible infections. Therapeutic anticoagulation [26] is preferred to prophylactic anticoagulation.
- Catheter-related infections are one of the most frequent and major complications [3, 5], especially in children under 2 years of age [6]. The most common focuses of infection are the skin flora in short duration catheters and the hub in permanent catheters. Blood spreading or solution contamination is rare. The most frequent microorganisms are *Staphylococcus epidermidis, Enterobacter* spp.*, E. coli, Klebsiella pneumoniae, Pseudomona aeruginosa, Staphyloccus aureus, Enterococcus (E. faecalis, E. faecium) y Candida albicans,* and other fungy. CVC-associated infection should be suspected if the child's temperature rises above 38.5 °C, presents metabolic acidosis, thrombocytopenia, or glucose homeostatic instability in the absence of any other focus of infection on exploration. Simultaneous blood cultures should be performed from peripheral and central blood drawn through each lumen of the catheter, and then broad-spectrum antibiotics should be given in accordance with the directions of each institution [27]. Once blood culture and antibiogram results are known, if necessary, the administration of antibiotics will be modified. The duration of treatment depends on the germ isolated. In long duration CVC, "antibiotic lock" may be made. Catheter will be removed if the septic state persists 48 h after starting the antibiotic treatment, with either documented fungi or polymicrobial infections or recurrent bacteremia. Prevention consists in strict following of aseptic techniques in CVC handling, including hand washing and use of sterile gloves [28–30].

Metabolic Complications

- Deficit or excess of fluid, macro and micronutrients are the most common [8]. It is important to adjust the nutrients and fluids to patients' needs also taking into account the enteral supply. Special care must be given to undernourished patients to prevent the refeeding syndrome [15].
- Growth retardation: prevention is essential [6]. Clinical, anthropometric, and biochemical check-ups must be made regularly.
- Metabolic bone disease: multifactorial cause, very frequent in long-term PN, is related to excess trace element inputs (aluminum, phosphorus, and vitamin D), macronutrients (amino acids), and energy.
- PN-associated liver disease (PNALD) in children usually manifests as cholestasis of variable clinical significance: from transitory growth of hepatic enzymes (particularly gamma glutamyl transpeptidase) and bilirubin in PN over 15-day duration to cirrhosis in long-term PN [31]. There is an increased risk of PNALD in cases of recurrent sepsis or malnutrition. Developmental factors include factors related to the underlying disease and patient characteristics (prematurity and low-birth weight, infection and/or chronic inflammation, use of hepatotoxic drugs, surgery [32], etc.); lack of enteral stimulation; bacterial overgrowth and factors associated with PN either due to excessive input (calories, amino acids or glucose, phytosterols, Mn, etc.) or shortage (essential fatty acids, taurine, carnitine, or choline). Management of this complication involves adjusting parenteral inputs, increasing enteral support, PN cycling, preventing or treating bacterial overgrowth, and using ursodeoxycholic acid [6].

Psychosocial Complications

Psychosocial complications derive from the severity of the child's underlying disease, need for frequent hospitalizations, complex medical equipment, and family's overprotection [5, 6]. To avoid these problems an attempt to normalize the patient's life should be intended. Home PN should be established whenever possible.

Medication Compatibility

Most patients with NP receive other intravenous medications. Other drugs could suffer action modifications or precipitate in the catheter lumen. Therefore, compatibility verification is imperative whenever an exclusive administration route for the NP is not available [33].

References

1. Mascarenhas MR, Enriquez L. What is pediatric nutrition support? In: Baker SS, Baker RD, Davis AM, editors. Pediatric nutrition support. Sudbury: Jones and Bartlett Publishers; 2007. p. 123–33.
2. Koretz RL, Lipman TO, Klein S. AGA technical review on parenteral nutrition. Gastroenterology. 2001;121:970–1001.
3. Martínez Costa C, Sierra C, Pedrón Giner C, et al. Nutrición enteral y parenteral en pediatría. An Esp Pediatr. 2000;52 Suppl 3:1–33.

4. Mason DG, Puntis JWL, McCormick K, et al. Parenteral nutrition for neonates and children: a mixed bag. Arch Dis Child. 2011;96:209–10.
5. Koletzko B, Goulet O, Hunt J, et al. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr. 2005;41 Suppl 2:S1–87.
6. Gomis Muñoz P, Gómez López L, Martínez Costa C, et al. Spanish Society of Parenteral and Enteral Nutrition; Spanish Society of Gastroenterology, Hepatology and Nutrition; Spanish Society of Hospital Pharmacies. Consensus on paediatric parenteral nutrition: a document approved by SENPE/SEGHNP/SEFH. Nutr Hosp. 2007;22(6):710–9.
7. Braegger C, Decsi T, Amil Dias J, et al. Practical approach to paediatric enteral nutrition: a comment by the ESPGHAN Committee on Nutrition. J Pediatr Gastroentrol Nutr. 2010;51:110–22.
8. Kerner JA. Parenteral nutrition. In: Walker WA, Watkins JB, Duggan C, editors. Nutrition in pediatrics. 3rd ed. London: BC Decaer Inc.; 2003. p. 957–85.
9. Collier S, Gura KM, Richardson DS, et al. Parenteral nutrition. In: Hendricks KM, Duggan CH, editors. Manual of pediatric nutrition. 4th ed. London: Bc Decker; 2005. p. 317–75.
10. ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr. 2002;26(1 Suppl):1SA–38.
11. Krishnamurthy G, Keller MS. Vascular access in children. Cardiovasc Intervent Radiol. 2011;34:12–24.
12. Lee OK, Johnston L. A systematic review for effective management of central venous catheters and catheter sites in acute care paediatric patients. Worldviews Evid Based Nurs. 2005;2:4–13. discussion 14–5.
13. Schofield W. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr. 1985;39C Suppl 1:5–41.
14. Joint FAO/WHO/UNU Expert Consultation. *Energy and protein requirements*. Technical Report Series 724. Geneva: WHO; 1985.
15. Shulman RJ, Phillips S. Parenteral nutrition in infants and children. J Pediatr Gastroenterol Nutr. 2003;36:587–607.
16. Duro D, Rising R, Cole C, et al. New equations for calculating the components of energy expenditure in infants. J Pediatr. 2002;140:534–9.
17. Dietz WH, Bandini LG, Schoeller D. Estimates of metabolic rate in obese and non obese adolescents. J Pediatr. 1991;118:146–9.
18. Hardy G, Puzovic M. Formulation, stability, and administration of parenteral nutrition with new lipid emulsions. Nutr Clin Pract. 2009;24(5):616–25.
19. Cober MP, Teitelbaum DH. Prevention of parenteral nutrition-associated liver disease: lipid minimization. Curr Opin Organ Transplant. 2010;15(3):330–3.
20. Baker SS, Baker RD. Parenteral nutrition. In: Walter WA, Goulet O, Leinman R, Herman M, Shneider L, Sanderso IR, editors. Pediatric gastrointestinal disease. 4th ed. Hamilton, Ontario: BC Decker Inc.; 2004. p. 1958–80.
21. Lehmann CU, Conner KG, Cox JM. Preventing provider errors: online total parenteral nutrition calculator. Pediatrics. 2004;113:748–53.
22. Mühlebach S, Franken C, Stanga Z. Working group for developing the guidelines for parenteral nutrition of The German Association for Nutritional Medicine. Practical handling of AIO admixtures - Guidelines on Parenteral Nutrition, Chapter 10. Ger Med Sci. 2009;7:18.
23. Kerner Jr JA, Garcia-Careaga MG, Fisher AA, et al. Treatment of catheter occlusion in pediatric patients. JPEN J Parenter Enteral Nutr. 2006;30(1 Suppl):S73–81.
24. Blaney M, Shen V, Kerner JA, et al. CAPS Investigators. Alteplase for the treatment of central venous catheter occlusion in children: results of a prospective, open-label, single-arm study (The Cathflo Activase Pediatric Study). J Vasc Interv Radiol. 2006;17(11 Pt 1):1745–51.
25. Doellman D. Prevention, assessment, and treatment of central venous catheter occlusions in neonatal and young pediatric patients. J Infus Nurs. 2011;34(4):251–8.
26. Baskin JL, Pui CH, Reiss U, et al. Management of occlusion and thrombosis associated with long-term indwelling central venous catheters. Lancet. 2009;374(9684):159–69.
27. O'Grady NP, Alexander M, Dellinger EP, et al. Healthcare Infection Control Practices Advisory Committee. Guidelines for the prevention of intravascular catheter-related infections. Am J Infect Control. 2002;30(8):476–89.
28. Raad II, Hohn DC, Gillbreth BJ, et al. Prevention of central venous catheter-related infections by using maximal sterile barrier precautions during insertion. Infect Control Hosp Epidemiol. 1994;15:231–8.
29. Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in diagnosis, prevention, and management. Lancet Infect Dis. 2007;7(10):645–57.
30. Bishay M, Retrosi G, Horn V, et al. Chlorhexidine antisepsis significantly reduces the incidence of sepsis and septicemia during parenteral nutrition in surgical infants. J Pediatr Surg. 2011;46(6):1064–9.

31. Kumpf VJ. Parenteral nutrition-associated liver disease in adult and pediatric patients. Nutr Clin Pract. 2006;21:279–90.
32. Arsenault DA, Potemkin AK, Robinson EM, et al. Surgical intervention in the setting of parenteral nutrition-associated cholestasis may exacerbate liver injury. J Pediatr Surg. 2011;46(1):122–7.
33. Barnett MI, Cosslett AG, Duffield JR, et al. Parenteral nutrition. Pharmaceutical problems of compatibility and stability. Drug Saf. 1990;5:101–6.

Chapter 19
Home Parenteral Nutrition

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Key Points

- Home parenteral nutrition is the treatment of choice for intestinal failure. It is safe and allows intestinal adaptation and digestive autonomy in most children.
- The candidate for home parenteral nutrition should be in a stable condition and requires a safe central venous catheter.
- Selection of the most appropriate venous access is based on the patient's vascular access history, venous anatomy, and the nature of the underlying disease.
- Instructing patients and families about home parenteral nutrition is highly demanding in terms of nursing time and commitment from patients and careers.
- The teaching program includes guidelines on catheter and pump care, and on the prevention, recognition, and management of complications.
- Home parenteral nutrition monitoring should include the evaluation of the administration technique, tolerance, and efficacy.

Keywords Pediatric home parenteral • Intestinal failure • Central venous catheter • Monitoring • Parenteral nutrition-associated liver disease • Quality of life • Training • Complications

Abbreviations

CVC	Central venous catheter
ESPEN	European Society for Clinical Nutrition and Metabolism
HPN	Home parenteral nutrition
IT	Intestinal transplantation

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PNALD	PN-associated Liver Disease
PN	Parenteral nutrition
QoL	Quality of life
SBS	Short bowel syndrome

History of Pediatric Parenteral Nutrition

Parenteral nutrition (PN) involves the administration of fluids and nutrients using routes other than the gut, although usually involves central venous catheters (CVC). Home PN (HPN) refers to instances where this nutritional support is administered in the patient's home. Although this form of treatment is expensive and complex, it facilitates patients' social rehabilitation, returning them to their home environment, reducing healthcare costs, and improving quality of life (QoL). Pediatric patients present specific technical characteristics, as not only should a proper nutritional status be maintained, but also optimal growth and development.

At the very beginning a major difficulty was patients' rapid development of phlebitis and thrombosis when using a peripheral vein. Although central vein cannulation was first described in the 1950s it was not till late 1960s when it was systematically used for infusion of nutrients [1]. First case of HPN took place in 1969 when Shils et al. in New York, USA, used PN for 7 months in a 37-year-old woman with a short bowel syndrome (SBS) [2]. Following this landmark, HPN extended widely in North America as well as in Canada, Australia, and different European countries (France 1970; United Kingdom late 1970s) [3]. First HPN registry for the United States and Canada was started under Prof. M Shils development between 1975 and 1983 [4]. In Europe through the Home Artificial Nutrition Working Group of the European Society for Clinical Nutrition and Metabolism (ESPEN), multinational surveys have been performed in 1993, 1997, and 2003 [5–7].

There are very few data about the incidence of HPN in infants and children in Europe. A survey performed in 1997 estimated an incidence around 4.9 (France) to 0.23 (Spain) patients/million inhabitants below 16 years [8]. Estimated incidence in France in 2004 was 5/million inhabitants/year. More recent data show great differences between countries and even centers (from 1.76 patients/million inhabitants to 44.4) [9, 10]

National registers are very useful to know trends, specific indications, efficiency of treatment, costs, and to plan how to better use available resources and improve QoL and quality of services [11].

Indications: Who Needs HPN?

The indications for long-term PN are all situations where enteral/oral nutrition cannot meet nutritional needs. A candidate for HPN should be in a stable, safe condition and need to have a safe central venous access placed [12]. HPN is recommended for children with primary or secondary intestinal failure (Table 19.1). The most frequent intestinal disorder is the SBS (secondary to necrotizing enterocolitis, gastroschisis, intestinal atresia, or volvulus), followed by gastrointestinal motility disorders, severe malabsorption syndromes (untreatable diarrhea by microvillic atrophy, intestinal dysplasia, or autoimmune enteropathy), and inflammatory bowel disease (especially Crohn's disease). The most common extraintestinal processes are those associated with tumor pathology (graft-versus-host disease, postirradiation or postchemotherapy enteritis) and congenital or acquired immune deficiencies. It may also be necessary in cases of cystic fibrosis, chronic liver disease with severe malnutrition prior to liver transplantation, etc. A multicenter European survey performed in 2003 showed that the most frequent causes were SBS (44%); chronic diarrhea (16%); pseudo-obstruction syndrome (8.3%), and

Table 19.1 Indications for home parenteral nutrition in infants and children

Primary digestive diseases
Short bowel syndrome
Congenital intestinal malformations including gut atresia
Mesenteric volvulus
Necrotizing enterocolitis in neonates
Inflammatory bowel disease
Severe mucosal damage
Autoimmune diarrhea
Congenital mucosal atrophy and other intractable hereditary diarrheas
Consequences of chemotherapy or radiation
Motility disorders
Pseudo-obstruction syndrome
Extensive gut aganglionosis
Intestinal, high output fistula
Protein-losing enteropathy
Nondigestive diseases causing malnutrition
Cystic fibrosis
Oncologic patients
Immune deficiency
Chronic organ failure: hepatic, renal, etc. as a preparation for transplantation

immune deficiency (5.4%) [13]. At least half of the pediatric patients included in an HPN program are under 1 year old [14].

In most cases, intestinal adaptation is achieved over time and HPN can be stopped. In certain diseases and when complications arise due to the use of HPN, intestinal transplantation (IT) may be recommended.

The unique specific contraindication is the lack of central venous access. Nevertheless, the inability of the child's caregivers to take care of HPN is a relative contraindication.

Practical Issues

To establish and supervise HPN, a multidisciplinary experienced team is needed. This should include at least one physician, who is ultimately responsible for the patient, a nurse and/or dietitian and a pharmacist, as well as other health-care professionals. Components of the team vary according to the characteristics and capabilities of each center [15, 16].

This team selects HPN candidates according to:

1. The underlying disease, likelihood of rehabilitation, and life expectancy. The condition determining PN must be stable and not improve with hospitalization. Prior to patient discharge, it is essential to check the tolerance and the safety of the treatment.
2. The estimated duration of support: although it is unclear whether there is a minimum, some authors believe it should be at least 30 days [17].
3. Family and social characteristics: the patient's family must be able and willing to provide care and to administer the treatment safely and effectively after proper training.
4. Availability of both hospital and family financial resources, enabling the provision of materials and care after discharge.

The team will conduct education and training in the HPN technique to parents and/or caregivers (and patients, age permitting). The team will also prescribe the treatment mode and monitor it.

Table 19.2 Fluid and electrolyte requirements in children

Age (years)	Water (mL/kg/d)	Na (mmol/kg/d)	K (mmol/kg/d)	Ca (mmol/kg/d)	P (mmol/kg/d)	Mg (mmol/kg/d)
<1	120–150	2–3	1–3	1.5–2.25	1.5–2.25	0.24–0.42
1–2	80–120	1–3	1–3	0.6–1.5	0.6–1.5	0.1–0.24
3–5	80–100	1–3	1–3	0.6–1.5	0.6–1.5	0.1–0.24
6–12	60–80	1–3	1–3	0.6–1.5	0.6–1.5	0.1–0.24
13–18	40–60	1–3	1–3	0.6–1.5	0.6–1.5	0.1–0.24

Table 19.3 Energy, glucose, lipid, and amino acid requirements in children

Age (years)	Total energy (kcal/kg/d)	Glucose (g/kg/d)	Lipids (g/kg/d)	Amino acids (g/kg/d)
<1	90–100	12–18	2–3	1.8–2.5
1–7	75–90	8–11	2–3	1.5–1.8
7–12	60–75	8–10	1.5–2.0	1.0–1.5
12–18	30–60	5–7	1.5–2.0	0.8–1.3

Requirements

Nutritional requirements should include disease-specific needs and factors to be considered include medical condition, nutritional status, level of activity, and organ function [12].

These requirements are established prior to the discharge of the patient and should be reviewed shortly after discharge in order to make appropriate modifications. When possible, resting energy expenditure should be measured to determine energy load.

Although it has been extensively described in Chap. 18 (Parenteral nutrition in infants and children) a summary of requirements for fluid, electrolytes, and macronutrients is presented in Tables 19.2 and 19.3.

For newborn and infants specific solutions should be used containing conditionally essential amino acids. D-glucose will be the exclusive supply of carbohydrates. Lipid emulsions are administered at 20% (MCT/LCT or mixed with olive oil or fish oil); it is essential to ensure a minimum supply of essential fatty acids. Some specialists restrict fat intake to three days a week in order to reduce the risk of liver complications. The use of ω3 is currently under study to reverse or reduce this problem [18].

Phosphorus requirements can be met without precipitation problems by using sodium glycerophosphate, which has proven effective and safe.

The optimal energy: nitrogen ratio in children is approximately 150–250:1. As most patients receive HPN in a cyclic regimen (see below), the rate of glucose delivery should not exceed 1.2–1.4 g/kg/h in an infant, 1.0–1.2 g/kg/h in a child 1–10 year old, and 0.5–0.8 g/kg/h in an adolescent [19].

Each PN infusion should provide water-soluble and lipid-soluble vitamins and trace elements according to the patient age, weight, and specific needs. They need to be adapted in case of kidney or liver dysfunction.

Venous Access. Venous Access Care

HPN usually requires a central venous access. Selection of the most appropriate access device is based on the patient's vascular access history, venous anatomy, and the nature of underlying disease [20]. Beside these factors, child's development, social and intellectual skills, activity level, body image concerns, and family function need to be assessed in the decision-making process [21].

Table 19.4 Central venous access for home parenteral nutrition in children and adults

Age	Tunneled catheters (F)	Ports
<1 year	2.7–4.2	Rarely used
1–3 years	3.0–5.0	Preferably a tunneled catheter
4–11 years	4.2–7.0	0.6–1.0 mm internal diameter
Adolescents	5.0–12.5	0.8–1.4 mm internal diameter
Adults	7.0–13.0	0.8–1.4 mm internal diameter

The most common CVC used are (Table 19.4):

(a) Partially implanted devices or tunneled catheters type Broviac® or Hickman®. The catheter is placed percutaneously in a central vein and tunneled from the access site to an exit site usually in the chest area or in the upper abdomen. If used only for HPN, one lumen catheters are preferred. One or two Dacron cuffs are located on the subcutaneous part of the catheter. These cuffs help to avoid accidental displacement as well as act as a barrier for bacteria from the skin.
(b) Totally implanted devices or subcutaneous ports (port-a-cath). A subcutaneous port consists of a catheter connected to a port or reservoir, placed subcutaneously. To get the port it is necessary to puncture the skin by means of a special needle (Huber needle). The needle does not damage the diaphragm, and the procedure can be repeated up to 2,000 times before the system needs replacement. Its main advantage is that body image is preserved; on the contrary, the major disadvantage is the need to puncture the skin daily.

More recently, peripherally inserted central venous catheters (PICC) have been used both in adult and pediatric patients, although the experience is limited.

No data are available for comparison of the use of implanted ports with tunneled catheters in terms of lifespan, complications, and QoL [12].

Line Care

A strict protocol should be followed regarding aseptic technique and staff training. The fundamentals are:

- The placement of such catheters must be performed under sterile conditions in an operating or interventional radiology room [22], under general or local anesthesia.
- It is preferable to use single-lumen catheters for PN because it reduces the incidence of infection.
- It is essential to secure catheters firmly, especially in infants and young children, to prevent accidental removal or dislodgement.
- Antiseptic washing of hands and use of sterile gloves is essential prior to handling the catheter.
- The transparent or gauze dressing covering the exit site should be changed once or twice per week, whenever it is dirty or when insertion point inspection is necessary.
- Vascular accesses should be kept permeable with heparin or saline, although it is unknown whether its efficacy is similar to that of adult patients.

Teaching Patients and Families

Careful patient selection is necessary prior to the commencement of family training. This selection is ideally done by a multidisciplinary team. Several factors must be considered at this moment: patient suitability, home assessment, duration of treatment, and who will fund the therapy.

Teaching patients and families about HPN demands a huge amount of nursing time and commitment from the patients and the carers [23]. Before starting training it is important that they are fully prepared physically and emotionally. Sometimes it can be beneficial to meet someone already on HPN.

The teaching program includes catheter care, preventing and recognizing complications, pump care, and managing complications. Instruction manuals, illustrations, or CD are used in most centers [24].

Training should start when the CVC has been placed. The duration of the training process is on average 2 weeks, where the patient or the caregiver can do everything by himself/herself by the second week.

On discharge it is stressed that the patient is not to be left alone, and a 24 h phone should be available.

Administration

HPN should be administered cyclically (10–18/24 h), adjusting to patient tolerance and infusing preferably overnight by volumetric pumps. Cyclic infusion has metabolic, physical, and psychological advantages [25]. A pump is indispensable for PN. Pumps should achieve a good compromise between safety and comfort (simplicity). All-in-one mixtures contained in a multilayered bag and 1.2 μm filters should be used. Both the bag and the line of administration during infusion should be protected from the light.

Although in some institutions the families have to go to the local hospital to get the mixtures as well as the ancillary sets, in most cases home care companies deliver them to the home. Currently, only a few standard formulas are suitable for children on HPN.

Monitoring

Follow-up of patients should include monitoring administration (daily volume of PN and other inputs, technique, and material used), tolerance (clinical and biochemical), detection and solution of complications (trouble-shooting, onset of intercurrent diseases), and PN efficacy (growth and body composition as well as biochemical parameters). Once discharged from hospital, a regular outpatient follow-up is planned according to each individual situation, initially at monthly intervals, more frequently if necessary, especially in infants. Table 19.5 outlines the main clinical and biochemical check-ups to be performed [16].

Complications

HPN is not free of complications. An important aspect is its prevention and early diagnosis, which will allow an appropriate treatment to be started quickly enough to avoid immediate and future consequences. Table 19.6 summarizes the main complications, which are described in detail in Chap. 18 (Parenteral nutrition in infants and children). Catheter obstruction, thromboembolism, catheter-related infection, and PN-associated liver disease are the most common and severe complications. Loss of vascular access is frequent in children under 2 years of age. In order to avoid aversion to oral feeding, it is important to maintain oral intake, mainly in infants. Finally, with the aim to prevent psychosocial consequences, patients should attend school and classes regularly whenever possible; similarly, they should get involved in extracurricular activities. In summary, the family unit and the patient's autonomy must be promoted and preserved.

Table 19.5 Clinical and laboratory monitoring of pediatric patients on home parenteral nutrition

Frequency (months)	Clinical assessment	Laboratory assessment and others complementary tests
1–3	Clinical examination	Complete blood count
	Weight, height/length, head circumference	Acid–base balance
	Mid-upper-arm circumference	Chemistry profile: glucose, serum electrolytes, urea, creatinine, total protein, albumin, prealbumin, lipid profile, calcium–phosphorous metabolism (calcium, phosphorus, magnesium, alkaline phosphatase), zinc, and iron metabolism
	Skinfold thickness	Liver function tests: aspartate amino transferase, alanine amino transferase, gamma glutamyl transpeptidase, total and direct bilirubin
	Dietary assessment	Study of coagulation
6–12	Idem	Vitamin levels (A, E, and D)
		Parathormone and thyroid hormones
		Hepatobiliary ultrasound
2–24	Ídem	Bone densitometry

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Table 19.6 Complications of home parenteral nutrition in infants and children

CVC related
Pneumotorax, vessel laceration, cardiac perforation, cardiac tamponade
Occlusion: external or internal (by lipid, mineral, and drugs deposits or blood)
Thromboembolism
Catheter-related infections
Metabolic complications
Deficit or excess of fluid, macro, and micronutrients
Growth retardation
Metabolic bone disease
PN-associated liver disease
Psychosocial complications
Feeding problems (food aversion)

Quality of Life

QoL is difficult to define and measure. Calman defined it as "a reflection of the difference at a given time between the hopes and expectations of an individual and the individual's present experience" [26]. There are very few specific questionnaires designed for HPN patients [27] Most of published reports use generic, validated questionnaires to compare HPN patients to a healthy population, while other use disease-specific instruments to investigate more specific issues. More recently a new HPN-specific questionnaire has been validated in Europe [28]. There are no specific questionnaires designed to assess QoL in children with HPN, so general questionnaires have been used in research [29]. One study addressed the QoL in children participating in the five existing HPN programs in France [30]. The results showed that their QoL was similar to that of the healthy reference population explored in all areas except those related to health. Same results have been observed in other studies [31]. An interesting finding was that siblings also revealed to have an average QoL. By contrast, mothers had a lower score for QoL than those of parents of healthy children, and also significantly lower than that of fathers in matters relating to work, home life, and feelings of freedom.

Legislation

No formal European policy has been developed or proposed to ensure safe, cost-effective, and patient-centered use of HPN although local guidelines even ESPEN guidelines have been published in recent years.

Regarding legislation, it differs between countries. Funding, on the contrary, is relatively uniform: national health systems support all the costs of HPN in Europe [32].

Outcomes and Future Perspectives

HPN is a safe therapy and is the treatment of choice for intestinal failure because it facilitates intestinal adaptation and digestive autonomy in most children [33]. However, the success of intestinal adaptation is compromised by certain circumstances which often fulfill the criteria for PN failure [34]: (1) difficulty in maintaining an adequate state of nutrition and hydration despite PN optimization; (2) impossibility of surviving without hospitalization due to complications; (3) development of severe PN secondary complications (PNALD, loss of venous access, recurrent sepsis, or metabolic disorders) [35]. Even in the cases with few or no complications arranging transition from the pediatric to the adult services is a challenging situation, both for the young people and their families [36].

Patients with intestinal failure are complex. Early referral to the Intestinal Rehabilitation and Transplantation Units for appropriate assessment could improve prognosis. Criteria for referral to these units are [34, 37, 38] liver dysfunction or high risk of developing it; preterm with massive intestinal resection; persistent hyperbilirubinemia (3–6 mg/dL); complex clinical problems (uncertain diagnosis, intestinal lengthening interventions); limitation on central venous access (difficulty in placement or maintenance); extensive venous thrombosis (2 of 4 higher venous accesses), or recurrent; frequent catheter sepsis, especially in patients with liver dysfunction.

In summary, although the number of pediatric patients receiving HPN is not great, better knowledge, organization, administration, and monitoring of this support technology by specially trained personnel and their timely referral to Intestinal Rehabilitation and Transplantation Units can improve the outcome for these children in all aspects.

References

1. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Can intravenous feeding as the sole means of nutrition support growth in the child and restore weight loss in an adult? An affirmative answer. Ann Surg. 1969;169:974–84.
2. Shils ME, Wright LM, Turnbull A, Brescia F. Long-term parenteral nutrition through an external arteriovenous shunt. N Engl J Med. 1970;283:324–44.
3. Elia M. History of parenteral nutrition. In: Bozzetti F, Staun M, van Gossum A, editors. Home parenteral nutrition. Oxon, United Kingdom: Cabi; 2006. p. 1–11.
4. Shils ME. The advent of home parenteral nutrition support. Annu Rev Nutr. 2010;30:1–12.
5. Van Gossum A, Bakker H, De Francesco A, et al. Home parenteral nutrition in adults: a multicentre survey in Europe in 1993. ESPEN-Home Artficial Nutrition Working Group. Clin Nutr. 1996;15:53–8.
6. Van Gossum A, Bakker H, Bozzetti F, et al. Home parenteral nutrition in adults: a European multicentre survey in 1997. ESPEN-home artificial nutrition working group. Clin Nutr. 1999;18:135–40.
7. Staun M, Moreno JM; Bozzetti F, et al. Home parenteral nutrition in adults: a European survey in 2003. Clin Nutr 2004;23(4):916(A326).
8. Van Gossum A, Colomb V, Hebuterne X, et al. Home parenteral nutrition (HPN) in children. A multicentre survey in Europe in 1997. Clin Nutr. 1998;17 Suppl 1:49.
9. Beath SV, Gowen H, Puntis JWL. Trends in paediatric home parenteral nutrition and implications for service development. Clin Nutr. 2011;30:499–502.

10. Juana-Roa J, Wanden-Berghe C, Sanz Valero J. The reality of home-based parenteral nutrition. Nutr Hosp. 2011;26:364–8.
11. Castelló-Botía I, Wanden-Berghe C, Sanz Valero J. Artificial nutrition support registries: systematic review. Nutr Hosp. 2009;24:711–6.
12. Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr. 2005;41 Suppl 2:S1–87.
13. Lyszkowska M, Moreno JM, Colomb V, et al. Experience in home parenteral nutrition in children from 15 European centers. Clin Nutr. 2004;23 Suppl 4:907.
14. Colomb V, Talbotec C, Goulet O, Corriol O, Lamor M, Ricour C. Outcome in children on long-term (home) parenteral nutrition: a 20-year experience. Clin Nutr. 2003;22:73–4.
15. A.S.P.E.N. Board of Directors and the Standards for Specialized Nutrition Support Task Force, Kovacevich DS, Frederick A, Kelly D, Nishikawa RA, Young L. Standards for specialized nutrition support: home care patients. Nutr Clin Pract. 2005;20:579–790.
16. Pedrón Giner C, Martínez Costa C, Gómez López L, et al. Home parenteral nutrition in children: procedures, experiences and reflections. Nutr Hosp. 2010;25:705–11.
17. Kerner JA, Hurwitz MH. Parenteral nutrition. In: Duggan CD, Watkins JB, Walker WA, editors. Nutrition in pediatrics. 4th ed. Hamilton: BC Decker Inc; 2008. p. 777–93.
18. Goulet O, Antébi H, Wolf C, et al. A new intravenous fat emulsion containing soybean oil, medium-chain triglycerides, olive oil, and fish oil: a single-center, double-blind randomized study on efficacy and safety in pediatric patients receiving home parenteral nutrition. J Parenter Enteral Nutr. 2010;34:485–95.
19. Lyszkowska M, Moreno Villares J, Colomb V. Home parenteral nutrition in children. In: Bozzetti F, Staun M, van Gossum A, editors. Home parenteral nutrition. Oxon, United Kingdom: Cabi; 2006. p. 325–41.
20. Chawls WJ. Vascular access for home intravenous therapy in children. J Parenter Enteral Nutr. 2006;30:S57–64.
21. Martínez Costa C, Sierra C, Pedrón Giner C, et al. Nutrición enteral y parenteral en pediatría. An Esp Pediatr. 2000;52 suppl 3:1–33.
22. Krishnamurthy G, Keller MS. Vascular access in children. Cardiovasc Intervent Radiol. 2011;34:12–24.
23. Gifford H, DeLegge M, Epperson LA. Education methods and techniques for training home parenteral nutrition patients. Nutr Clin Pract. 2010;25:443–50.
24. Gómez López L, Gutiérrez Suárez M. Programa de nutrición parenteral domiciliaria pediátrica. Cuaderno de información para las familias. Valencia: Gráficas Diamante; 2008. ISBN 84-691-5079-5. http://www.nadya-senpe.com/public/elementos.htlm
25. Stout SM, Cober MP. Metabolic effects of cyclic parenteral nutrition infusion in adults and children. Nutr Clin Pract. 2010;25:277–81.
26. Calman KC. Quality of life of cancer patients—an hypothesis. J Med Ethics. 1984;10:124–7.
27. Winkler MF. Quality of life in adult home parenteral nutrition patients. J Parenter Enteral Nutr. 2005;29:162–70.
28. Baxter JP, Fayers PM, McKinlay AW. The development and translation of a treatment-specific quality of life questionnaire for adult patients on home parenteral nutrition. e-SPEN. 2008;3:e22–8.
29. Pane S, Solans M, Gaite L, Serra-Sutton V, Estrada MD, Rajmil L. Instrumentos de calidad de vida relacionada con la salud en la edad pediátrica. Revisión sistemática de la literatura: actualización. Agència d'Avaluació de Tecnología i Recerca Mèdiques. Barcelona; 2006.
30. Gottrand F, Staszewski P, Colomb V, et al. Satisfaction in different life domains in children receiving home parenteral nutrition and their families. J Pediatr. 2005;146:793–7.
31. Emedo MJ, Godfrey EI, Hill SM. A qualitative study of the quality of life of children receiving intravenous nutrition at home. J Pediatr Gastroenterol Nutr. 2010;50:431–40.
32. Moreno Villares JM, Leon SM. Legislation on home parenteral nutrition. In: Bozzetti F, Staun M, van Gossum A, editors. Home parenteral nutrition. Oxon, United Kingdom: Cabi; 2006. p. 364–71.
33. Gandullia P, Lugani F, Costabello L, et al. Long-term home parenteral nutrition in children with chronic intestinal failure: a 15-year experience at a single Italian center. Dig Liver Dis. 2011;43:28–33.
34. Beath S, Pironi L, Gabe S, et al. Collaborative strategies to reduce mortality and morbidity in patients with chronic intestinal failure including those who are referred for small bowel transplantation. Transplantation. 2008;85:1378–84.
35. Sauvat F, Fusaro F, Lacaille F, et al. Is intestinal transplantation the future of children with definition intestinal insufficiency? Eur J Pediatr Surg. 2008;18:368–71.
36. Protheroe S. Symposium 6: young people, artificial nutrition and transitional care. Transition in young people on home parenteral nutrition. Proc Nutr Soc. 2009;68:441–5.
37. Fecteau A, Atkinson P, Grant D. Early referral is essential for successful pediatric small bowel transplantation: the Canadian experience. J Pediatr Surg. 2001;36:681–4.
38. Kaufman SS, Atkinson JB, Bianchi A, et al. Indications for pediatric intestinal transplantation: a position paper of the American Society of Transplantation. Pediatr Transpl. 2001;5:80–7.

Chapter 20
The Role of Colonic Flora in Infants

Carlos H. Lifschitz

Key Points

- Factors influencing the characteristics of the fecal flora, fecal flora and disease, role of carbohydrate fermentation, short chain fatty acids, and gas as a by-product of carbohydrate fermented in the colon

Keywords Short chain fatty acids • Fecal flora • Intestinal fermentation • Probiotics • Intestinal bacteria

Introduction

At birth, the intestine is sterile and colonic function of the human infant is immature. The development of the colonic function (i.e., water absorption and carbohydrate fermentation) is related in part to that of the bacterial flora. The role of the bacterial flora (intestinal microbiota) has evolved in recent years and in addition to the metabolic functions that was known to perform, an important inmunoregulatory role has been established and the human microbiome project has been launched with the goal of identifying and characterizing the microorganisms which are found in association with both healthy and diseased humans. Modulation of the fecal flora by probiotics is the topic of active investigation. The role of the flora in health and disease is no longer a hypothesis. Characteristics of the flora have been implicated in as causing or perpetuating acute and chronic illnesses that may extend into adulthood. Products of carbohydrate fermentation have also been seen to play a regulatory role in the life cycle of the colonocyte, the epithelial cell of the colon. Both in infants and adults, a variable proportion of dietary carbohydrate is not absorbed in the small bowel and arrives in the colon where it undergoes bacterial fermentation. The products of this fermentation are short-chain fatty acids (SCFAs), principally acetate, propionate, and butyrate [1], together with gases such as CO_2, hydrogen (H_2), and methane (CH_4). A fraction of these products are absorbed through the colonic mucosa into the circulatory system; butyrate is utilized by the epithelial cells of the colon [2]; the rest is expelled through the anus as stools or flatus [3].

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Development of the Intestinal Flora

In the first year of life, the infant intestinal tract progresses from intestinal sterility at birth to extremely dense colonization, ending with a mixture of microbes that is broadly very similar to that found in the adult intestine [4]. The majority of the fecal studies in infants have employed the classical plating techniques with culturing on specific media [5]. These methods present some limitations considering the diversity of the bacterial flora. Newer techniques have added some information to the existing knowledge.

The maternal intestinal flora is a source of bacteria for the neonatal gut. The bacterial flora is usually heterogeneous during the first few days of life, independently of feeding habits. After the first week of life, a stable bacterial flora is usually established. In full-term infants a diet of breast milk induces the development of a flora rich in *Bifidobacterium* spp. Other obligate anaerobes, such as *Clostridium* spp. and *Bacteroides* spp., are more rarely isolated and also enterobacteria and enterococci are relatively few. During the corresponding period, formula-fed babies are often colonized by other anaerobes in addition to bifidobacteria and by facultatively anaerobic bacteria; the development of a "bifidus flora" is unusual. In other studies the presence of a consistent number of bifidobacteria in infants delivered in large urban hospitals has not been demonstrated, whether the babies were bottle fed or exclusively breast fed. The predominant fecal bacteria were coliforms and bacteroides. According to these studies, environmental factors may be more important than breastfeeding in gut colonization after delivery. Environmental factors are indeed extremely important for the intestinal colonization of infants born by cesarean section. In these infants, the establishment of a stable flora characterized by a low incidence of *Bacteroides* spp. and by the isolation of few other bacteria is consistently delayed. In extremely low-birth weight infants, hospitalization in neonatal intensive care units, characterized by prolonged antibiotic therapy, parental nutrition, delayed oral feedings, and intubation seems to affect the composition of the intestinal microbiota.

The gut is colonized by a small number of bacterial species; *Lactobacillus* and *Bifidobacteria* spp. are seldom, if ever, identified. According to the few studies so far performed, the predominant species are *Enterococcus faecalis*, *E. coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, and *Staphylococcus haemolyticus*. Hygienic conditions and antimicrobial procedures strongly influence the intestinal colonization pattern. However, Harmsen et al. using molecular identification of colonies of fecal bacterial cultures from six samples obtained in the first 20 days of life from six breast-fed and six formula-fed newborn infants [6] reported that qualitative information from the culturing results combined with the data obtained by the FISH technique revealed initial colonization in all infants of a complex (adult-like) flora. After this initial colonization, a selection of bacterial strains began in all infants, in which Bifidobacterium strains played an important role. In all breast-fed infants, bifidobacteria become dominant, whereas in most formula-fed infants similar amounts of Bacteroides and bifidobacteria (approximately 40%) were found. The minor components of the fecal samples from breast-fed infants were mainly lactobacilli and streptococci; samples from formula-fed infants often contained staphylococci, *Escherichia coli*, and clostridia. Additional data come from a larger study on which fecal samples from 1,032 infants recruited from the KOALA Birth Cohort Study in the Netherlands were cultured at 1 month of age [7]. The authors found that the most important determinants of the gut microbiotic composition in infants were the mode of delivery, type of infant feeding, gestational age, infant hospitalization, and antibiotic use by the infant. Term infants who were born vaginally at home and were breast fed exclusively seemed to have the most "beneficial" gut microbiota (highest numbers of bifidobacteria and lowest numbers of *C. difficile* and *E. coli*).

Impact of Gut Microbiota on Gut Maturation, the Immune System, and Disease

Influence of Bacterial Colonization on the Immune System

Authors have speculated that there could be an association between the characteristics of colonic bacterial flora early in the first few postnatal months and the development of certain diseases later in life. It is known that among infants sensitized to some allergen(s), those with high, as compared with low levels, of salivary secretory IgA (SIgA) are less likely to develop allergic symptoms [8]. Sjögren et al. found that the number of Bifidobacterium species in the early infant fecal samples correlated significantly with the total levels of salivary SIgA at 6 months of age [9, 10]. Early colonization with *Bifidobacterium* species, lactobacilli groups, or *C. difficile* did not influence toll like receptors (TLR) 2 and 4 expression in peripheral blood mononuclear cells (PBMCs). However, PBMCs from infants colonized early with high amounts of Bacteroides fragilis expressed lower levels of TLR4 mRNA spontaneously. Furthermore, lipopolysaccharide-induced production of inflammatory cytokines and chemokines, e.g. IL-6 and CCL4 (MIP-1 beta), was inversely correlated to the relative amounts of Bacteroides fragilis in the early fecal samples. The same authors also found that children who by 5 years of age had developed allergy were significantly less often colonized with lactobacilli group I (*Lactobacillus* (*L.*) *rhamnosus*, *L. casei*, *L. paracasei*), *Bifidobacterium adolescentis*, and *C. difficile* during their first 2 months of life [9, 10].

An interesting hypothesis has come forth in 2003 and has since found additional support from several other publications [11] and that is the association between birth by cesarean section and development of allergy. In a population-based birth cohort of 2,803 children, information regarding mode of delivery, maternal or infant use of antibiotics, and information on potential confounders was obtained prospectively from parental reports and the Norwegian Birth Registry. Parentally perceived reactions to egg, fish, or nuts, as well as objectively confirmed reactions to egg at the age of 2½ years, were chosen as outcomes. Results indicated that among children whose mothers were allergic, cesarean section was associated with a sevenfold increased risk of parentally perceived reactions to egg, fish, or nuts (odds ratio, 7.0; CI, 1.8–28; $P=0.005$) and a fourfold increased risk of confirmed egg allergy (odds ratio, 4.1; CI, 0.9–19; $P=0.08$) in a logistic regression analysis, adjusting for pregnancy complications, birth weight, gestational length, and socioeconomic factors. Among children whose mothers were not allergic, the association was much weaker and not significant. Maternal or infant use of antibiotics was not associated with an increased risk of food allergy. Laubereau et al. studied a total of 865 healthy full-term neonates with parental history of allergy that participated in the prospective German Infant Nutritional Intervention Program (GINI) [12]. Infants were exclusively breast fed during the first four months of life and had a one year follow-up. It was found that infants born by cesarean section (147/865, 17%) had a greater risk of diarrhea (OR(adj) 1.46, 95% CI 1.022–2.10) and sensitization to food allergens, both in adjusted (OR(adj) 2.06, 95% CI 1.123–3.80) and stratified analyses (by cord blood IgE). Cesarean delivery was not associated with colicky pain and atopic dermatitis. Several other studies have corroborated this finding [13, 14] but not all [15].

Modulation of the Fecal Flora by Probiotics and its Potential Health Benefits

Probiotics are live human-derived organisms which impart a health benefit to the host. Consumption of "good" bacteria in our diets results in the transient changes in the bacteria in our intestinal tract. There is a growing and probably justifiable skepticism of the advertising claims for many natural and

food products; therefore, the ability to educate consumers about good bacteria is somewhat limited [16]. Clinical studies have validated the used of probiotics for the following conditions: viral diarrhea, antibiotic-associated diarrhea, *C. difficile*-associated diarrhea, traveler's diarrhea, atopic dermatitis, pouchitis, irritable bowel syndrome, and infantile colic [17]. *L. acidophilus, Lactobacillus* GG, *Lactobacillus reuteri,* and *Saccharomyces boulardii* are the most studied probiotics. Probiotics have been used in single strands or in a combination.

Biochemistry of Carbohydrate Fermentation

The term *short-chain fatty acid* is really a misnomer as these acids, although indeed have a short chain of carbons, are not really fatty but are chemically closer to carbohydrates than to fat [18]. The term *volatile fatty acids* is not, however, a better descriptor of its characteristics. The name comes from the fact that originally these acids were measured by steam distillation following acidification of the intestinal contents and, therefore, were volatile. More modern methods of separation such as gas–liquid chromatography resulted in that name being abandoned. Acetate, propionate, and butyrate are moderately strong acids, with an average pK value of 4.8. In the intestine, they exist as negatively charged anions and not as free acids. When ionized, SCFAs are not volatile. When carbohydrate arrives in the colon, fermentation reactions occur. As a result, colonic lumenal pH decreases while the concentrations of ammonia, short- and long-chain fatty acids, and bile acids increase. The bacteria capable of fermenting carbohydrate are mainly anaerobes or facultative aerobes [19]. The process of carbohydrate fermentation requires for the colonic bacterial flora to be present in a high enough concentration and that the lumenal pH be in accordance to the bacterial pK (6 or greater). Therefore, it is obvious that newborns are incapable of carbohydrate fermentation to the level achieved by older infants and adults.

Actinomyces Bacteroides

Another situation in which carbohydrate fermentation is decreased or even abolished is during treatment with broad-spectrum antibiotics [20] or when large amounts of carbohydrate are malabsorbed daily because the lumenal pH fails below the bacterial pK [21]. The not uncommon finding of reducing substances in the stools of infants during the first few days of life due to the presence of intact carbohydrate can be explained by the fact that a fraction of the dietary carbohydrate that is malabsorbed by the small bowel cannot be fully fermented and transformed into SCFAs. This is also reflected by the low breath H_2 levels [22]. Similarly, despite the fact that the infants are malabsorbing carbohydrate, the fecal pH may be 6 or higher. Special types of bacteria are necessary to produce propionate, H_2, and CH_4, and to the extent that they are needed, not every individual is capable of producing them [23]. For example, CH_4 is generally not produced in the first years of life. Rutili et al. [24] studied fecal samples from children between 3 months and 5 years for the presence of methanogenic bacteria. Methanobacteria were not detected in fecal samples obtained from children under 27 months of age. At 27 months, only one subject harbored methanobacteria; the number of methanobacteria hosts subsequently increased with age, with an incidence of 40% at 3 years and 60% at 5 years. The appearance of methanobacteria was not directly related to the introduction of particular foods in the child's diet. These dietary changes could give rise to some physical–chemical modifications of the enteric lumen, thus causing the conversion of the intestinal flora to an adult pattern and, in most subjects, the development of methanobacteria.

SCFAs are known to enhance intestinal growth and function in animal models of resection [25] and in humans with ulcerative colitis [26]. As well, they may play an important role in the intestine after

surgery [25]. Of the products of fermentation of carbohydrate, butyrate contributes to the energy needs of the colonic epithelial cell [2]. The process of carbohydrate fermentation and absorption of its products is known as "colonic scavenging." Acetate and to a lesser extent propionate are absorbed into the system and, at least in ruminants, contribute a significant amount to the energy needs of the host [27]. SCFAs and butyrate in particular have effects on epithelial cells. Butyrate inhibits proliferation and promotes differentiation of several colonic epithelial cell lines [28], alters cell morphology [29], and even influences synthesis and secretion of several proteins [30]. SCFAs promote cell migration [31]. The preferential substrate for the *colonocyte,* the cell that constitutes the mucosal lining of the colon, is butyrate.

Fitch and Fleming [32] determined the influence of substrate concentration and substrate interactions on SCFA metabolism in an animal model. When the luminal concentrations of butyrate were increased 20-fold, linear increases in total C resulted, but CO_2 production from butyrate increased as a function of concentration only up to a certain point and was stable at higher butyrate concentrations, indicating a saturation process in the capacity of the colon to further utilize butyrate. The presence of a mixture of alternative substrates in the lumen had no influence on the metabolism of butyrate to CO_2, but significantly reduced the metabolism of acetate to CO_2, when compared with young (4-month-old) animals, transport of butyrate was significantly lower for aged (48-month-old) animals. These results show that important aspects of SCFA transport and metabolism are not predicted from data using isolated colonocytes but require study using an in vivo model.

Because it was not known whether colonocytes in the newborn can metabolize butyrate, this was examined in the newborn and infant rat colon [33]. Isolated colonocytes from rats of different perinatal ages were incubated with 14C-labeled butyrate or glucose in vitro. Complete oxidation was estimated by the production of 4C-labelled CO_2, whereas intermediate metabolites were measured enzymatically. Oxidation of butyrate was highest in newborns, declining at day 10 and even further in adult rats. Glucose oxidation was also highest at birth, with a minor increase at approximately day 20 (weaning period) before decreasing to adult levels. Butyrate oxidation was substantially higher than was glucose oxidation in all age groups. The authors concluded that neonatal rat colon epithelial cells resemble adult colonocytes in their preference for butyrate as a metabolic substrate, indicating a constitutive expression of this property.

Of interest is the fact that the normal microflora of the large intestine synthesizes biotin and that the colon is capable of absorbing intraluminally introduced free biotin. To understand the mechanism of biotin absorption in the large intestine and its regulation, Said et al. [34] used a human-derived, nontransformed, colonic-epithelial cell line. The initial rate of biotin uptake was found to be temperature and energy dependent, Na^+ dependent saturable as a function of concentration, and competitively inhibited by the vitamin pantothenic acid. These results point to the functional existence of a Na^+-dependent, specialized, carrier-mediated system for biotin uptake in colonic-epithelial cells. This system is shared with pantothenic acid.

Role of the Colonic Flora

The fate of dietary carbohydrate in the infant and the adult is that, even under physiological conditions, a certain proportion of the ingested carbohydrate, particularly complex ones such as starches, escape complete digestion by pancreatic and mucosal enzymes and thus absorption by the small bowel, therefore arriving in the large bowel. In the case of most infants, until cereals are introduced into the diet, the carbohydrate incompletely absorbed is lactose. Recent studies indicate that the fraction of carbohydrate malabsorbed by breast-fed infants could be the oligosaccharides present in breast milk [35]. In the presence of a functioning colonic flora, the unabsorbed carbohydrate is fermented according to a series of well-defined reactions that depend on the type of bacteria present. The composition of the

colonic flora depends on such things as the way the infant was delivered [36, 37], whether they were term or preterm [36, 38], the diet [39–42], and ill-defined influences. The introduction of additional food items results in changes in the bacterial enzyme activity [43]. By the eighth postnatal day, *Bacteroides fragilis* can be isolated from the stool of more than 50% of formula-fed, term infants delivered vaginally [31]. Possibly because of contamination that occurs during passage through the birth canal, infants delivered vaginally have significantly higher fecal isolates of anaerobic bacteria and *Bacteroides fragilis* in particular than those delivered by cesarean section. Moreover, in the study by Long and Swenson [36], it was demonstrated that gestational age also affects colonization of the bowel, so that by 7 days of age, preterm infants have significantly less anaerobic bacteria isolated from stools than those born full term. This finding could be related to the fact that term infants are larger and spend a longer time in contact with maternal fluids in the birth canal. The type of feeding also played a role in determining the establishment of the fecal flora, an effect that becomes apparent by the seventh day of life. By the third day of life both breast-fed and formula-fed infants have similar bacterial counts of *Bacteroides fragilis,* other anaerobic bacteria, aerobic gram-negative bacilli, and streptococci. By the end of the first week, however, only 22% of breast-fed infants have *Bacteroides fragilis* isolated from the stools compared to 61% of the formula-fed counterparts.

The fecal flora is also affected by iron supplementation [44]. In a study that compared the prevailing bacteria in the fecal flora of infants, it was seen that in contrast to breast-fed infants in whom bifidobacteria predominated and in whom counts of *E. coli* were low and other bacteria were rarely present, infants who were fed an Fe-fortified cow-milk formula had high counts of *E. coli* and low counts and isolation frequency of bifidobacteria. In addition, many other kinds of bacteria were frequently isolated in the Fe supplemented, formula-fed infants. Other studies have demonstrated that stools of breast-fed infants who have also received formula or cow milk acquire certain characteristics not observed in samples from exclusively breast-fed infants [41, 44]. Such differences include higher fecal pH and production of propionate, a SCFA which is virtually absent in feces of exclusively breast-fed infants [45].

The role of the colon on carbohydrate scavenging in the newborn has been the attention of several studies. In one of them, sequential studies of breath H2 excretion in response to lactose feeding were carried out in 22 premature infants during the first 7 weeks of life [46]. Seventy-five percent of infants excreted H_2 in breath during the first 2 weeks; 100% did so by the end of the third week. The peak H_2 concentration and the 5-h mean breath H_2 excretions were significantly related to lactose intake per day. Calculations using the 5-h mean H_2 excretion allowed the authors to estimate that 66% or more of ingested lactose entered the colon and was fermented. Throughout the studies, stool patterns and rates of weight gain of the infants were normal. In another study, Kien et al. [47] measured carbohydrate energy absorption and breath H_2 concentration in 12 premature infants at 28–32 weeks gestational age and 2–4 weeks postnatal age. Infants received one of two formulas that differed only in carbohydrate source: one contained 100% lactose (LAC) and the other 50% lactose:50% glucose polymers (LAC + GP). In 11 of the 12 infants studied, there was evidence of extensive colonic fermentation as suggested by the breath H_2 levels. An approximate 100% increase in lactose intake in the LAC group was associated with a similar increase in breath H_2 concentration. None of the infants exhibited diarrhea or vomiting or developed delayed gastric emptying. The mean ± standard deviation calculated carbohydrate energy absorption was, respectively, 86 ± 5% and 91 ± 3% in the LAC and the LAC + GP groups. The authors concluded that colonic bacterial fermentation may be critical to energy balance and to the prevention of osmotic diarrhea in premature infants fed lactose. From these and other studies it can be concluded that premature infants normally malabsorb substantial amounts of lactose. The elevation of breath H_2 observed in these infants, however, apparently represents a successful adaptation of the colonic microflora to this physiological malabsorption and should not be cause to modify the diet of an infant who is clinically well.

With the purpose of identifying aspects of the process of carbohydrate fermentation that could differ between breast-fed and formula-fed infants, the authors performed an in vitro study of carbohydrate fermentation by the fecal flora of both of the above groups of infants [45]. The authors incubated fecal

samples from breast-fed and formula-fed infants under different conditions: pH 6.8 and 5.5, with and without the addition of lactose, to simulate the fecal pH observed in cases of complete carbohydrate absorption in the small bowel in the former and that of malabsorption in the latter. The effect of acid pH on bacterial fermentation and changes in carbohydrate fermentation in relation to the age of the infant were also studied. At pH 6.8, which is within the normal range, addition of lactose resulted in a significant increase in the production of SCFAs and larger amounts of lactose, glucose, and galactose compared with what was found in incubates to which no lactose was added. Irrespective of the diet, when stools were incubated at pH 5.5, which is the pH found in stools of infants with carbohydrate malabsorption, SCFA production was significantly lower compared to what occurred at pH 6.8. At the acid pH, accumulation of glucose and galactose in the incubate of feces of formula-fed infants increased significantly compared to what occurred at the alkaline pH. In contrast, incubates at pH 5.5 of stools from breast-fed infants resulted in a greater proportion of lactose as a result of a decrease in the amount of lactose hydrolyzed. The decrease in lactose hydrolysis in breast-fed infants resulted in a lower osmolality of the incubate which, if it also were to occur in vivo, could provide a partial explanation for the fact that stool output in cases of carbohydrate malabsorption such as in acute gastroenteritis is milder in this population. This is an example of how diet may affect the way that malabsorbed carbohydrate is handled by the colon.

Edwards et al. [48] measured the concentration of fecal SCFA in babies fed breast milk or infant formula from birth. Their study corroborated the knowledge that breast-fed infants have significantly lower fecal pH values at week 2 and 4 than formula-fed infants. These authors found no difference, however, in the amount of fecal water between the two dietary groups. As opposed to Lifschitz et al. [45], Edwards et al. found that the concentration of SCFA was not different between the two groups. However, in agreement with Lifschitz et al. they demonstrated higher fecal concentration of propionic, as well as *N*-butyric and isovaleric acids, and also confirmed the predominance of lactic and acetic acid in the feces of breast-fed infants. Of interest is the fact that breast-fed infants produce very little *N*-butyrate, a SCFA that is known to be the preferential nutrient of the mature colonocyte.

As the infant matures and the fecal flora develops, new metabolic products appear in feces. Norin et al. [49] used the concept of microflora-associated characteristics (MAC), which they defined as the identification of an anatomical structure or biochemical or physiological function in the host that is influenced by the microflora. Several of these MACs were identified. Only in the second year of life could intestinal bacteria convert bilirubin to urobilin, degrade mucin, and convert cholesterol. Tryptic activity was not demonstrated in meconium, was present in feces from all children studied up to 21 months of age and, for reasons that are not apparent, absent in 6 out of 15 children in the age group of 46–61 months. The relevance of this study is that it demonstrated that the establishment of the full metabolic capacity of the bacterial flora is a considerably extended process. Another indicator of maturation of the fecal flora can be exemplified by the fact that most infants and young children cannot produce CH_4, as stated before [24].

It is known that SCFA play a role in water homeostasis in the colon. However, because of the inaccessibility of this organ, precise data in humans is difficult to obtain. The transport of sodium has been studied in the infant colon [50]. Absorption of SCFA and its effects on water and sodium conservation by the colon were studied in pigs and shown to be age dependant [51]. Maximal absorption of SCFA was seen at birth, followed by a rapid decline over 72 h to a lower and relatively stable level. Water and sodium absorption increased with age and the addition of SCFA to the experimental perfusion solution resulted in further enhancement in the first 2 weeks of life. After the fourteenth day of life, sodium absorption continued to be enhanced by addition of SCFA, but water absorption remained unchanged from control levels, suggesting that although lumenal SCFA levels may be limited early in life, their presence has stimulatory effects on the absorption of sodium and water in the colon of newborns. The development of the fecal flora has very important practical implications such as regulation of water absorption in the colon. The capacity of the colon to compensate for the excessive arrival of fluid as it occurs in gastroenteritis was studied by Argenzio et al. [52]. In this study, maximal water absorption capacity was compared between 3-day-old and 3-week-old pigs infected with

transmissible gastroenteritis virus. The older animals exhibited a compensatory response to the excess water inflow to the colon and were able to increase up to six times the capacity to absorb fluids compared to the younger animals to the point that diarrhea was completely prevented. Moreover, the 3-week-old pigs were able to ferment to SCFA all carbohydrate that arrived in the colon completely, whereas in the younger pigs carbohydrate passed through the colon unchanged and appeared in feces. This study demonstrated that development of microbial digestion together with rapid SCFA absorption is a primary feature responsible for the colonic compensation observed as a factor of age.

As stated before, broad-spectrum antibiotic treatment results in a considerable decrease of the colonic bacterial flora and consequently the capacity to ferment dietary carbohydrate that arrives in the colon and may explain the diarrhea that frequently occurs in infants treated with such drugs [53]. Whenever the amount of carbohydrate arriving in the colon is relatively large, colonic fermentation (which can be monitored by the production of H_2) and SCFA become clinically relevant. This can be the case with gastroenteritis or a large amount of carbohydrate and or carbohydrates that cannot be completely digested such as when a relatively large amount of certain fruit juices or beverages containing a high concentration of carbohydrate are administered [54]. Although much has been said about fruit juice and carbohydrate malabsorption, the authors have demonstrated that at lower, reasonable volumes of juice intake, carbohydrate absorption is not a problem [55].

Excessive colonic fermentation as a consequence of carbohydrate malabsorption or by a characteristic of the fecal flora has been considered to be one of the causes of infantile colic. Moore et al. [56] performed breath H_2 tests following a lactose challenge in infants with colic. They concluded that among the infants that they studied, colicky infants produced more H_2 in both the fasted state and after the ingestion of formula. The authors considered that lactose malabsorption, differences in colonic bacterial fermentation conditions, or a difference in the way that the H_2 produced was handled (i.e., absorbed vs. excreted by flatus) could explain the differences observed between colicky and noncolicky infants. Another study, however, failed to demonstrate a significant difference in the amount of H_2 produced by colicky and noncolicky babies [57].

Over the years, multiple studies have addressed the potential positive effects of colonization with *Lactobacillus* species (e.g., CG). *Lactobacillus* is considered to be a probiotic, that is a living organism capable of exerting health benefits beyond inherent basic nutrition. An interesting example is the effect of *Lactobadllus* CC on shortening the duration of acute diarrhea in children [58].

As an interesting concept in the process of development of the colon, it is known that the feces of 40–70% of newborn infants harbor *Clostridium difficile* and toxin B [59] in concentrations similar to those found in adults with pseudomembranous colitis. However, most newborn infants experience no symptoms. Possible explanations for this state of asymptomatic carrier in infants include:

1. Absence of enterotoxin A, the toxin responsible for pathogenesis
2. Absence of colonic receptors
3. Diminished inflammatory response

Again, differences were found based on the type of nutrition: infants fed formula were nearly four times more likely to carry *Clostridium difficile* than were those exclusively breast fed (62% vs. 16%). Breast-fed infants who were also receiving formula or solids had an intermediate rate of colonization (35%) [59].

Discussion

Fermentation of carbohydrate in the large bowel results in the production of acids and gas. It may also result in increased water in the lumen of the bowel. The products of carbohydrate fermentation play an important role in assuring the welfare of the colonocytes. SCFAs are known to enhance intestinal

growth and function in animal models of resection and in humans with inflammatory bowel disease. As well, they may play an important role in the intestine after surgery. Butyrate, one of the SCFAs produced during the fermentation of dietary fiber, is a potent inducer of differentiation of tumor cells, and it has been speculated that it may account for the protective effects of certain types of fiber for colonic tumourogenesis. In the infant under physiological conditions, particularly if breast fed, a moderate amount of carbohydrate arrives in the colon and is fermented by the bacterial flora. The fact that fermentation of carbohydrate takes place and is almost complete is evidenced by the finding of H_2 breath, the lack of reducing substances in stools, and an increased amount of SCFAs although fecal pH remains above 5.5. Whenever the amount of carbohydrate arriving in the colon exceeds the capacity of the bacterial flora to ferment it, carbohydrate appears in the stool. Another possibility is that when the amount of SCFA produced is greater than that which can be absorbed by the colon, fecal pH falls. This is particularly true for lactic acid, which diffuses through the colonic mucosa less well than the other acids. Infants with an incompletely developed colonic flora or those receiving antibiotics, which destroy the flora, may not be able to handle excessive amounts of nonabsorbed dietary carbohydrate and develop diarrhea. Older infants produce gas in the colon when fermentation of carbohydrate takes place, which leads to discomfort, irritability, or even crying spells. However, a certain amount of SCFA may be necessary for the welfare and regulation of cell proliferation of the colonocytes. It is therefore important to determine the right amount, if any, of nonabsorbable carbohydrate that infants may ingest without developing symptoms.

References

1. Cummings H, Macfarlane GT. Role of intestinal bacteria in nutrient metabolism. Parenter Enteral Nutr. 1997;21:357–65.
2. Roediger WE. Oxidative and synthetic functions of n-Butyrate in colonocytes. Dis Colon Rectum. 1992;35(5):511–2.
3. Levitt MD, Engel RR. Intestinal gas. Adv Intern Med. 1975;20:151–65.
4. Palme C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLoS Biol. 2007;5(7):177.
5. Fanaro S, Chierici R, Guerrini P, Vigi V. Intestinal microflora in early infancy: composition and development. Acta Paediatr Suppl. 2003;9:48–55.
6. Harmsen HJ, Wildeboer-Veloo AC, Raangs GC, Wagendorp AA, Klijn N, Bindels JG, et al. Analysis of intestinal flora development in breast-fed and formula-fed infants by using molecular identification and detection methods. J Pediatr Gastroenterol Nutr. 2000;30:61–7.
7. Penders J, Thijs C, Vink C, et al. Factors influencing the composition of the intestinal microbiota in early infancy. Pediatrics. 2006;118:511–21.
8. Sandin A, Björkstén B, Böttcher MF, Englund E, Jenmalm MC, Bråbäck L. High salivary secretory IgA antibody levels are associated with less late-onset wheezing in IgE-sensitized infants. Pediatr Allergy Immunol. 2011;22:477–81.
9. Sjögren YM, Tomicic S, Lundberg A, Böttcher MF, Björkstén B, Sverremark-Ekström E, et al. Influence of early gut microbiota on the maturation of childhood mucosal and systemic immune responses. Clin Exp Allergy. 2009;39:1842–51.
10. Sjögren YM, Jenmalm MC, Böttcher MF, Björkstén B, Sverremark-Ekström E. Altered early infant gut microbiota in children developing allergy up to 5 years of age. Clin Exp Allergy. 2009;39:518–26.
11. Eggesbø M, Botten G, Stigum H, Nafstad P, Magnus P. Is delivery by cesarean section a risk factor for food allergy? J Allergy Clin Immunol. 2003;112:420–6.
12. Laubereau B, Filipiak-Pittroff B, von Berg A, Grübl A, Reinhardt D, Wichmann HE, et al. Caesarean section and gastrointestinal symptoms, atopic dermatitis, and sensitisation during the first year of life. Arch Dis Child. 2004;89:993–7.
13. Koplin J, Allen K, Gurrin L, Osborne N, Tang ML, Dharmage S. Is caesarean delivery associated with sensitization to food allergens and IgE-mediated food allergy: a systematic review. Pediatr Allergy Immunol. 2008;19:682–7.
14. Sánchez-Valverde F, Gil F, Martinez D, Fernandez B, Aznal E, Oscoz M, et al. The impact of caesarean delivery and type of feeding on cow's milk allergy in infants and subsequent development of allergic march in childhood. Allergy. 2009;64:884–9.

15. Kvenshagen B, Halvorsen R, Jacobsen M. Is there an increased frequency of food allergy in children delivered by caesarean section compared to those delivered vaginally? Acta Paediatr. 2009;98:324–7.
16. Federal Trade Commission, US Food and Drug Administration. "Miracle"health claims: add a dose of skepticism. 2001. Available at: http:// www.ftc.gov/bcp/edu/pubs/consumer/health/hea07.shtm. Accessed 14 Dec 2007.
17. Vanderhoof J, Young R. Probiotics in the United States. Clin Infect Dis. 2008;46 Suppl 2:S67–72.
18. Wrong OM. Definitions and history. In: Physiological and clinical aspects of short-chain fatty acids the large bowel. In: Cummings JH, Rombeau JL, Sakata T, editors. Physiological and clinical aspects of short-chain fatty acids. Cambridge: Cambridge University Press; 2005. p. 1–14.
19. Macfarlane GT, Gibson GR. Microbiological aspects of the production of short-chain fatty acids in the large bowel. In: Cummings JH, Rombeau JL, Sakata T, editors. Physiological and clinical aspects of short-chain fatty acids. Cambridge: Cambridge University Press; 1995. p. 87–106.
20. Gilat T, Ben Hur H, Geiman-Malachi E, Terdiman R, Peled Y. Alterations of the colonic flora and their effect on the hydrogen breath test. Gut. 1978;19:602–5.
21. Perman A, Modler S, Olson AC. Role of pH in production of hydrogen from carbohydrates by colonic bacterial flora Studies in vivo and in vitro. J Clin Invest. 1981;67:643–50.
22. Stevenson DK. Breath hydrogen in preterm infants. Am J Dis Child. 1989;143(11):1262–3.
23. Strocchi A, Levitt MD. Factors affecting hydrogen production and consumption by human fecal flora. The critical roles of hydrogen tension and methanogenesis. J Clin Invest. 1992;89(4):1304–11.
24. Rutili A, Canzi E, Brusa T, Ferrari A. Intestinal methanogenic bacteria in children of different ages. New Microbiol. 1996;19(3):227–43.
25. Tappenden KA, Thomson AB, Wild GE, McBurney MI. Short-chain fatty acid-supplemented total parenteral nutrition enhances functional adaptation to intestinal resection in rats. Gastroenterology. 1997;112(3):792–802.
26. Breuer RI, Soergel KH, Lashner BA, Christ ML, Hanauer SB, Vanagunas A, et al. Short chain fatty acid rectal irrigation for left-sided ulcerative colitis. A randomised, placebo controlled trial. Gut. 1997;40:485–91.
27. Martin SA. Nutrient transport by ruminal bacteria: a review. J Anim Sci. 1994;72:3019–31.
28. Basson MD, Turowski GA, Rashid Z, Hong F, Madri A. Regulation of human colonic cell line proliferation and phenotype by sodium butyrate. Dig Dis Sci. 1996;41:1989–93.
29. Scheppach W, Mullcr JC, Boxberger E, Dusel G, Richter F, et al. Histological changes in the colonic mucosa following irrigation with short-chain fatty acids. Eur J Gastroenterol Hepatol. 1997;9(2):163–8.
30. Frankel W, Lew J, Su B, Bain A, Kiurfeld D, Einhorn E, et al. Butyrate increases colonocyte protein synthesis in ulcerative colitis. J Surg Res. 1994;57:210–4.
31. Wilson AJ, Gibson PR. Short-chain fatty acids promote the migration of colonic epithelial cells in vitro. Gastroenterology. 1997;113(2):487–96.
32. Fitch MD, Fleming SE. Metabolism of short-chain fatty acids by rat colonic mucosa in vivo. Physiology. 1999;277:G31–40.
33. Krishnan S, Ramakrishna BS. Butyrate and glucose metabolism in isolated colonocytes in the developing rat colon. J Pediatr Gastroenterol Nutr. 1998;26:432–6.
34. Said HM, Ortiz A, McCloud E, Dyer D, Moyer MP, Rubin S. Biotin uptake by human colonic epithelial NCM460 cells: a carrier-mediated process shared with pantothenic acid. Am J Phvsiol. 1998;275(5 pt 1):C1365–71.
35. Brand-Miller JC, McVeagh P, McNeil Y, Messer M. Digestion of human milk oligosaccharides by healthy infants evaluated by the lactulose hydrogen breath test. J Pediatr. 1998;133:95–8.
36. Long SS, Swenson RM. Development of anaerobic fecal flora in healthy newborn infants. J Pediatr. 1977;91:298–301.
37. Groniund MM, Lehtonen OP, Eerola E, Kero P. Fecal micro flora in healthy infants born by different methods of delivery. Permanent changes in intestinal flora after cesarean delivery. J Pediatr Gastroenterol Nutr. 1999;28:19–25.
38. Sakata H, Yoshioka H, Fujita K. Development of the intestinal flora in. Very low birth weight infants compared to normal full-term newborns. Eur J Pediatr. 1985;144(2):186–90.
39. Langhendries JP, Detry J, Van Hees J, Lamboray JM, Darimont J, Mozin MJ, et al. Effect of a fermented infant formula containing viable bifidobacteria on the fecal flora composition and pH of healthy full-term infants. Acta Paediatr Scand. 1985;74:45–51.
40. Lundequist B, Nord CE, Winberg J. The composition of the faecal microflora in breastfed and the role of colonic fermentation in infants bottle fed infants from birth to eight weeks. Eur J Pediatr. 1985;144:186–90.
41. Balmer SE, Scott PH, Wharton BA. Diet and faecal flora in the newborn: Casein and whey proteins. Arch Dis Child. 1989;64:1678–84.
42. Kleessen B, Bunke H, Tovar K, Noack J, Sawatzki G. Influence of two infant formulas and human milk on the development of the faecal flora in newborn infants. Acta Paediatr. 1995;84:1347–56.
43. Mykkanen H, Tikka J, Pitkanen T, Hanninen O. Fecal bacterial enzyme activities in infants Increase with age and adoption of adult-type diet. J Pediatr Gastroenterol Nutr. 1997;25(3):312–6.
44. Balmer SE, Wharton BA. Diet and faecal flora in the newborn: Iron. Arch Dis Child. 1991;66:1390–4.

45. Lifschitz CH, Wolin MJ, Reeds PJ. Characterization of carbohydrate fermentation in feces of formula-fed and breast fed infants. Pediatr Res. 1990;27:165–9.
46. MacLean Jr WC, Fink BB. Lactose malabsorption by premature infants: magnitude and clinical significance. J Pediatr. 1980;97:383–8.
47. Kien CL, Liechty EA, Myerberg DZ, Mullett MD. Dietary carbohydrate assimilation in the premature infant: evidence for a nutritionally significant bacterial ecosystem in the colon. Am J Clin Nutr. 1987;46:456–60.
48. Edwards CA, Parrett AM, Balmer SE, Wharton BA. Faecal short chain fatty acids in breast-fed and formula-fed babies. Acta Paediatr. 1994;83:459–62.
49. Norin KE, Gustafsson BE, Lindblad BS, Midtvedt T. The establishment of some microflora associated biochemical characteristics in feces from children during the first years of life. Acta Paediatr Scand. 1985;74(2):207–12.
50. Jenkins HR, Schnackenberg U, Milla PJ. *In vitro* studies of sodium transport in human infant colon: the influence of acetate. Pediatr Res. 1993;34:666–9.
51. Murray RD, McClung HJ, Li BU, Ailabouni A. Stimulatory effects of short-chain fatty acids on colonic absorption in newborn piglets in vivo. J Pediatr Gastroenterol Nutr. 1989;8:95–101.
52. Argenzio RA, Moon HW, Kemeny LJ, Whipp SC. Colonic compensation of transmissible gastro-enteritis in swine. Gastroenterology. 1984;86:1501–6.
53. Bhatia J, Prihoda AR, Richardson CJ. Parenteral antibiotics and carbohydrate intolerance in term neonates. Am J Dis Child. 1986;144:111–3.
54. Lifschitz CH. Carbohydrate absorption from fruit juices in infants. Pediatrics. 1999
55. Smith MM, Davis M, Chasalow EL, Lifschitz E. Carbohydrate absorption from fruit juice in young children. Pediatrics. 1995;95(3):340–4.
56. Moore DJ, Robb TA, Davidson GP. Breath hydrogen response to milk containing lactose 111 colicky and noncolicky infants. J Pediatr. 1988;113:979–84.
57. Hyams JS, Geertsma MA, Etienne NL, Treem WR. Colonic hydrogen production in infants with colic. J Pediatr. 1989;115:592–4.
58. Isolauri E, Juntunen M, Rautanen T, Sillanaukee P, Koivula T. A human L*actobacillus* strain *(Lactobacillus* casei sp strain GG) promotes recovery from acute diarrhea in children. Pediatrics. 1991;88:90–7.
59. Coopersrock M, Riegie L, Woodruff CW, Onderdonk A. Influence of age, sex, and diet on asymptomatic colonization of infants with *Clostridium difficle*. J Clin Microbiol. 1983;17:830–3.

Chapter 21
Pro- and Prebiotics for the Prevention and Treatment of Diseases in Childhood

Elisabeth Haschke-Becher and Ferdinand Haschke

Key Points

- Microbiota contributes to the nutritional welfare of the human host through metabolism of complex dietary carbohydrates, generation of short-chain fatty acids as energy substrate for colonic epithelia, and production of folate and B vitamins.
- Probiotics have been defined as nonpathogenic, live, viable microorganisms which, upon ingestion in sufficient numbers, alter the microflora.
- Prebiotics, like fructo- and galacto-oligosaccharides, benefit the host by selectively stimulating the favorable growth and/or activity of selected probiotic bacteria in the colon.
- Probiotics were shown to be efficient for the treatment of acute infectious diarrhea to reduce duration and stool frequency, although optimal probiotic strain and dosage for individual patient groups still remain to be determined.
- For the prevention of diarrhea in children with most pro- and prebiotics, data are too limited for conclusions.
- No recommendations for the use of pro- and prebiotics for the treatment of Helicobacter pylori infections, inflammatory bowel disease, and for the prevention of allergies can be done at present.
- The use of clinically tested products with pro- and/or prebiotics such as follow-up formula, growing-up milks, and cereals after 6 months of age is considered to be safe.

Keywords Probiotics • Prebiotics • Infectious Diarrhea • *Helicobacter pylori* • Inflammatory bowel disease • Safety

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Introduction

Children have ten times more microbial than body cells. Most of them are located within the gastrointestinal tract, the so-called gut microbiota. So far, more than 500 different species have been identified with microbiological techniques. However, there are probably many more as might soon be revealed by the Human Microbiome Project (HMP), which was started in 2007 by the National Institute of Health employing new molecular technologies, such as meta-genomics and high-through-put sequencing which no longer require traditional cell culture. The human microbiome is the collective genome of all microorganisms present in the human body and on its surface. Remarkable differences in the microbiota of human beings have already been shown. One of the goals of the HMP was to understand whether changes in the human microbiome are associated with changes in health status.

It has long been known that the microbiota contributes to the nutritional welfare of the human host through metabolism of complex dietary carbohydrates, generation of short-chain fatty acids as energy substrate for colonic epithelia, and production of folate and B vitamins. In addition, the influence on the developing immune system has been established since the first experiments with germ-free animals more than half a decade ago. More recently, it became also clear that the immune response of the human host has reciprocal effect on the composition of microbiota. Diet and elements of modern lifestyle such as changes in social structure, urbanization, reduced amount of infections, etc. are associated with changes in microbiota which may contribute to the increased risk of allergic and metabolic diseases in developed countries. Preclinical and clinical studies have provided evidence linking the interaction of immune system and microbiota with the risk of metabolic syndrome [1], obesity [2], and type 1 diabetes [3]. Recently, Wang et al. [4] showed that dietary fat and intestinal microbiota may translate into an increased risk of atherosclerosis. The concept of manipulating the gut microbiota during and beyond infancy for the prevention or treatment of diseases, including those that become manifest in later life, is appealing. However, long-term consequences of such a manipulation need to be evaluated.

One method of modulating the intestinal flora consists of administration of so-called probiotics via food (follow-up formulas, growing-up milks, yoghurts) or supplements. Probiotics have been defined as nonpathogenic, life, viable microorganisms which, upon ingestion in sufficient numbers, alter the microflora. Those were shown to have clearly identifiable positive effects on health or disease [5–7]. Probiotics must resist normal digestion to reach the colon alive. The most commonly studied and used species of probiotics belong to the genera *Lactobacillus* (*L. rhamnosus* GG (LGG), *L. reuteri*, *L. johnsonii* La1, *L. salivarius* CECT5713), *Bifidobacterium* (*B. lactis* CNCMI 3446 ATCC55730), *Streptococcus* (*S. thermophilus*), and *Saccharomyces*. It must be pointed out that different probiotics have different properties and effects. The term "probiotics" is comparable to the term "antibiotics," which covers different categories of drugs endowed with different antibiotic activities. Some probiotics have been studied and used to prevent or treat infections and others may add value in the prophylaxis or treatment of allergic or inflammatory diseases [8]. Inherent biological features may enable probiotics to predominate over potentially pathogenic bacteria in the intestinal tract. They can create metabolic by-products such as short-chain fatty acids and butyrate, which exert beneficial regulatory influence and may function as immune modulators in the host [9, 10]. However, a wide variety of probiotic products for children are on the market without proven evidence of safety and efficacy.

Another approach of modulating the intestinal gut flora is the addition of nondigestible oligosaccharides, so-called prebiotics, to food products, beverages, or dietary supplements. Prebiotics benefit the host by selectively stimulating the favorable growth and/or activity of selected probiotic bacteria in the colon, in particular Bifidobacteria [6, 11]. Examples of prebiotics with clinical trials in children are fructo- and galacto-oligosaccharides and inulin. Finally, the combination of both pro- and prebiotics may be added to a food product, as so-called synbiotics. Studies on synergies between pre- and

probiotics so far have not yet been conclusive. Human milk, which is fed to children in developing countries until 2–3 years of age, contains >100 different oligosaccharides, bifidobacteria, and lactobacilli in a concentration of 10^3 to 10^4 per mL [12–14]. Preliminary reports on immunomodulatory effects of probiotics in breast milk are promising [14, 15].

Prevention and Treatment of Infectious Diarrhea

Gastroenteritis is the most common infectious disease in children. Despite vaccination campaigns in many countries rotavirus is still the most common cause of severe diarrhea, but other viruses, bacteria, and parasites induce enteritis and colitis in children as well. The impact of probiotic strains on infectious diarrhea has been studied in many well-designed clinical trials and meta-analyses. The mechanisms by which probiotics prevent and shorten infectious diarrhea are not well understood. They may compete with causative pathogens for binding sites, strengthen the mucosal barrier by enhancing mucosal secretory IgA production [16–18], increase specific IGA concentration in fecal samples [18], or act through molecular mechanisms [8].

A moderate effect of certain probiotic strains, such as LGG, *L. reuteri*, *L. salivarius* CECT5713, *Bifidobacterium lactis*, and *Streptococcus thermophilus* in the prevention and treatment of infectious diarrhea in children has been shown in randomized controlled trials and meta-analyses. Evidence has recently been reviewed by two independent Pediatric Nutrition Committees (ESPGHAN [19, 20]). Most studies were conducted in child care centers both in developed and developing countries. Children received probiotic strains with milk-based formulas or as supplements. Interesting are studies where selected strains were evaluated, because only commercial products with one strain or fixed mixes can be prescribed.

Prevention

Four studies using *Bifidobacterium lactis* as single strain or in combination [21–24] showed a significant reduction in the risk of nonspecific gastroenteritis (RR: 0.43; 95%CI 0.27–0.69; meta-analysis Fig. 21.1). One positive study each is available for *L. reuteri* ATCC55730 [24], for *L. salivarius* CECT5713 [25], for *L. casei* [26], and for LGG [27].

Treatment

In the year 2000, a large multicenter clinical trial [28] with 140 children revealed the addition of LGG at $\geq 10^{10}$ colony forming units (CFU)/250 mL to oral rehydration solution (ORS) to be efficacious for treatment of diarrhea in children <3 years of age. Duration of diarrhea after enrollment was 58 ± 28 h with ORS + LGG vs. 72 ± 36 h with ORS (mean ± SD; $P = 0.03$). Duration in the subgroup of rotavirus-positive children was 56 ± 17 vs. 77 ± 42 h ($P < 0.008$). Diarrhea lasted longer than 7 days in 2.7 and 10.7% of children with and without LGG, respectively ($P < 0.01$). Hospital stays were significantly shorter in the group with LGG. Other studies confirmed addition of LGG to ORS to reduce duration of acute diarrhea in children by 1 day, to lower the risk of a protracted course, and to result in faster discharge from hospital [20, 29]. Similarly, the addition of *L. reuteri* ATCC55730 reduced the duration

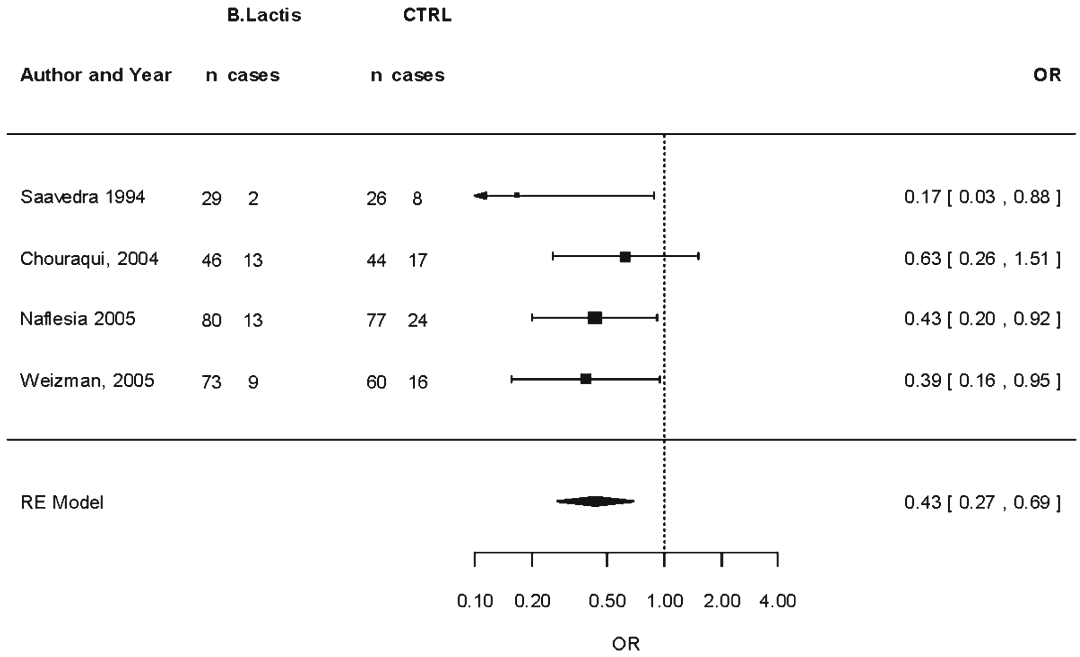

Fig 21.1 Meta-analysis comparing the effect of addition of *Bifidobacterium lactis* as single strain or in combination to infant formula on reduction in the risk of nonspecific gastroenteritis. The relative risk of 0.43 suggests that compared with no addition, *Bifidobacterium lactis* reduces the risk by 57%

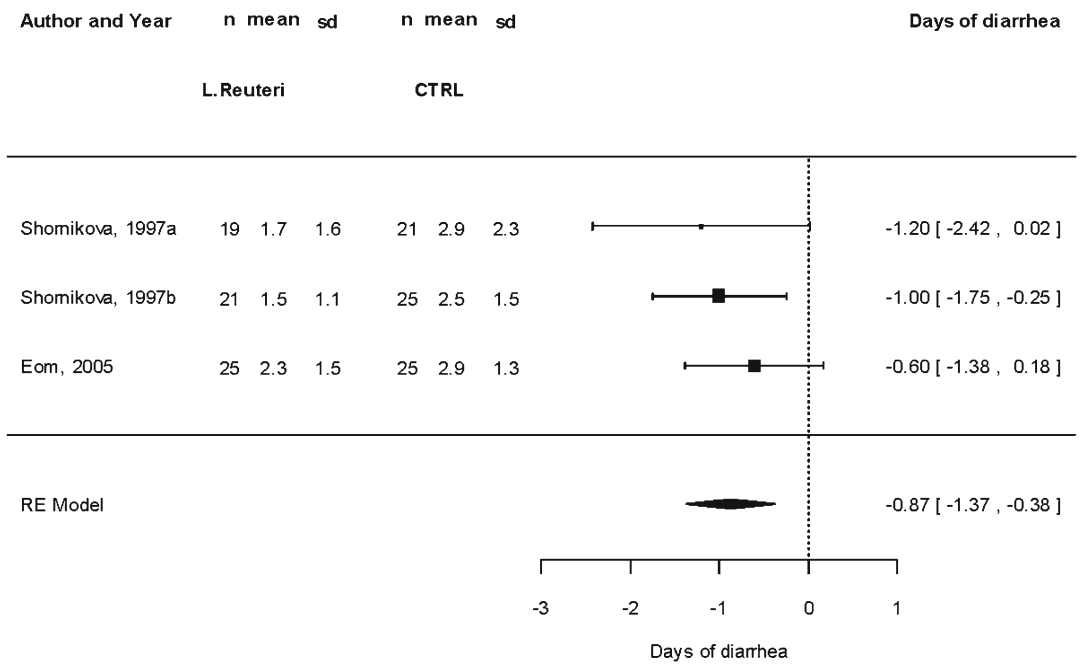

Fig 21.2 Meta-analysis comparing the effect of *L. reuteri* on duration of diarrhea. The RR of −0.87 suggests that compared with no addition, the use of *L. reuteri* reduces the duration by 0, 87 days (i.e., 22 h)

of diarrhea by 21 h (RR −0.87; 95% CI −1.37 to 0.39; meta-analysis Fig. 21.2; [30–32]). However, it is not clear whether benefit is specific only to the strains LGG and *L. reuteri*, as a recent systematic review indicated that several strains might be beneficial: 63 studies in a total of 8,014 patients were identified in which probiotic strains were used during oral rehydration therapy for treatment of acute diarrhea [29]. Of these, 56 trials recruited infants and young children. The trials were undertaken in a wide range of settings, greatly varied in tested strains, dosage, and patient characteristics. Probiotics reduced the duration of acute diarrhea, although the effect size varied considerably among studies. The effect was significant for the duration of diarrhea (mean difference 24.8 h; 95%CI 15.9–33.6 h; $n = 4{,}555$, trials=35), the risk of diarrhea lasting ≥4 days (RR: 0.41; 95%CI 0.32–0.53; $n = 2{,}853$, trials=29), and stool frequency on day 2 (mean difference 0.80; 95%CI 0.45–1.14; $n = 2{,}751$, trials=20). The differences in effect size were not explained by study quality, probiotic strain, the number of different strains, viability or dosage of organisms, the cause or severity of diarrhea, or whether studies were run in developed or developing countries. Authors concluded that several probiotic strains which were tested seem to have beneficial effects in acute infectious diarrhea by reducing duration and stool frequency. However, it was not clear which probiotic strain and dosage was most efficacious for specific patient groups.

Persistent diarrhea lasting for more than 14 days accounts for one third of diarrhea-related deaths of children in developing countries. Four randomized controlled trials enrolling a total of 464 children were identified to evaluate probiotic strains for treating persistent diarrhea in children [33]. Probiotics reduced the duration of persistent diarrhea and stool frequency, as shown in a meta-analysis of two trials ($n = 324$, mean difference 4.0 days, 95%CI 3.4–4.6 days). One trial reported significantly shorter hospital stay, but numbers were small. Thus, there is still limited evidence suggesting a specific probiotic strain to be effective in the treatment of persistent diarrhea in children.

Prebiotics

In 1993, a small study in 34 Peruvian infants showed some evidence that addition of dietary fiber (soy polysaccharide) to infant formula can ameliorate diarrheal stools [34]. However, the study was not statistically powered to prove the effect. Moore [35] evaluated the tolerability and gastrointestinal effects of FOS-supplemented infant cereal used as addition to the daily diet of healthy infants. Mean FOS consumption was 0.7 (SD 0.4) g/day reaching up to a maximum of 3.0 g/day. FOS consumption led to more regular and softer stools without diarrhea, as well as to less-reported frequency of symptoms associated with constipation such as hard stools or days without stool. No effect on prevention of diarrhea was shown.

Three publications of one study group which investigated the effects of the administration of an extensively hydrolyzed whey-based infant formula supplemented with GOS/FOS [36–38] were recently reviewed by ESPGHAN [19]. The GOS/FOS supplemented formula was associated with a number of beneficial health outcomes but not with a reduction in diarrheal episodes which was a secondary endpoint. There are no randomized clinical trials with prebiotics in children with diarrhea prevention or treatment as primary endpoint [20, 39]. Therefore, no recommendation on the use of prebiotics for prevention and treatment can be made at present.

Prevention of Antibiotic-Associated Diarrhea

Diarrhea is a common side effect if antibiotics are given orally or parenterally. Meta-analyses of clinical trials show controversial results regarding the efficacy of probiotics for the prevention of AAD. One focused on pediatric patients and identified six randomized controlled trials [40]. Treatment with

probiotics compared with placebo reduced the risk of (Antibiotic-Associated Diarrhea) AAD from 28.5 to 11.9% (RR: 0.44, 95%CI 0.25–0.77). A predefined subgroup analysis showed that risk reduction of AAD was associated with the use of *B. lactis* and *S. thermophilus* (1 trial, 157 participants, RR 0.5, 95%CI 0.3–0.95), LGG (2 trials, 307 participants, RR 0.3, 95%CI 0.15–0.6), or *S. boulardii* (1 trial, 246 participants, RR 0.2, 95%CI 0.07–0.6) [23]. Based on this analysis the Nutrition Committee of the AAP concluded that there is evidence of a beneficial effect. [20]. However, those findings are not in line with the last Cochrane database review [41] which was based on 10 independent pediatric trials, 6 with single strains and 4 with a combination of 2 strains. Nine of these studies reported a reduction in the incidence of diarrhea. However, based on an intention-to-treat (ITT) analysis probiotics had no effect (RR 0.90, 95% CI 0.50–1.63) due to significant dropout. Similarly, a recent meta-analysis on the efficacy of different Lactobacillus probiotic strains in preventing AAD showed no clear effect [42]: 10 randomized, blinded, placebo-controlled trials were considered. A total of 1,862 patients received either Lactobacillus at total daily doses of $2–40 \times 10^9$ CFU or placebo throughout the entire antibiotic treatment (5–14 days). Four studies included pediatric patients with age ranging from 2 weeks to 14 years. The relative risk of developing AAD was significantly lower with *Lactobacillus*, but in the subgroup of pediatric patients the effect was not significant (RR: 0.44, 95%CI 0.18–1.08). No clear recommendation can be made until results are confirmed through independent studies with clear-cut primary endpoints, in particular with the most promising strains *B. lactis*/*S. thermophilus*, LGG, and *S. boulardii*.

Helicobacter pylori Eradication

Helicobacter pylori is a highly prevalent pathogen, a major cause of chronic gastritis and peptic ulcer, and a risk factor for gastric malignancies. *H. pylori* eradication treatment with antibiotics is 90% effective. However, it is expensive and causes side effects and antibiotic resistance. Probiotics might be a low-cost, large-scale alternative to prevent or treat *H. pylori* colonization. Interest in probiotics is driven by clinical data showing efficacy of some probiotic bacteria and the rising demand of consumers for "natural" therapies [43].

Since first studies have indicated that the ingestion of milk supplemented with *Lactobacillus acidophilus* La1 can downsize *H. pylori* infection and gastritis in adults [44], there has been a continuous interest to demonstrate the therapeutic effect of probiotics. Seven out of nine studies in adults showed an improvement of *H. pylori* gastritis and decrease in *H. pylori* density after administration of probiotics [45]. Use of probiotics as an adjunct to standard antibiotic treatment significantly improved *H. pylori* eradication rates (81% vs. 71% with antibiotic alone; $p = 0.03$) and also significantly reduced *H. pylori* therapy-associated side effects (23% vs. 46%, with antibiotic alone; $p = 0.04$). Effects are often difficult to compare due to heterogeneity of studies regarding the employed probiotic strains, doses, and formulations. Based on current literature probiotics are unlikely able to eradicate *Helicobacter pylori* but might be useful as adjuvant in adults [43].

One recent meta-analysis also considered pediatric patients [46]. Five randomized controlled trials included a total of 1,307 participants among them 90 children. Compared with placebo or no intervention, *S. boulardii* given concomitantly to triple therapy significantly increased the eradication rate (four RCTs, $n = 915$, RR: 1.13, 95%CI 1.05–1.21) and reduced the risk of overall *H. pylori* therapy-related adverse effects (five RCTs, $n = 1305$, RR: 0.46, 95%CI 0.3–0.7), particularly of diarrhea (four RCTs, $n = 1{,}215$, RR: 0.47, 95%CI 0.32–0.69). No detailed analysis for the pediatric subgroup was possible. The authors concluded that there is some evidence to recommend the use of *S. boulardii* along with standard triple therapy to increase eradication rates and decrease side effects, particularly diarrhea. However, the evidence-based guidelines for *Helicobacter pylori* infection in children by

ESPGHAN and NASPHAN as of 2011 do not mention probiotic strains as part of eradication therapy [47]. In addition, limited data on prevention do not allow any recommendation.

Inflammatory Bowel Disease

Experimental and clinical research which has recently been reviewed [8, 15] indicates loss of immunological tolerance of the intestinal microbiota to be an important factor in the etiology of Crohn's disease (CD) and perhaps also of ulcerative colitis (UC). The discovery of the role of intestinal microbiota in the onset of inflammatory bowel disease (IBD) increased the interest to therapeutically modulate the intestinal flora of patients. It is estimated that about 40–70% of children and adults suffering from UC and CD use probiotics as either adjunct or replacement therapy [48, 49]. The administration of probiotics to adults with mild to moderate chronic UC has effects comparable to the treatment with anti-inflammatory drugs, such as mesalamine [50]. In particular, three clinical questions were evaluated in those studies which included some pediatric patients: maintenance of antibiotic-induced remission, treatment of acute active pouchitis, and prophylaxis of postoperative pouchitis. Pouchitis is a nonspecific inflammation in the ileal pouch which is used as reservoir after colectomy due to UC. A mix of four different Lactobacilli, three strains of Bifidobacteria, and one strain of Streptococcus thermophilus (VSL#3; Sigma-Tau Pharmaceuticals, Gaithersburg, MD) was tested in a randomized controlled trial. Remission through antibiotic treatment was achieved in all patients within 4 weeks. However, 17 out of 20 patients receiving probiotics were still in remission after 9 months follow-up whereas all patients in the placebo group had relapsed [51]. Whereas a second trial of the same group confirmed the results with the same mix of probiotics [52], a study with LGG showed no effect [53]. A meta-analysis of five RCTs indicated that probiotic strains can be effective in the management of pouchitis (OR: 0.04; 95%CI 0.01–0.14) [54].

In a RCT, children with newly diagnosed UC were given the VSL#3 mix along with corticosteroid induction therapy and mesalamine maintenance therapy. Remission was induced in 93 and 36% of the pediatric patients receiving and not receiving probiotics, respectively ($p<0.001$) and 23 and 73% patients, respectively, relapsed within 1 year (RR: 0.32; 95%CI 0.25-0.77; [55]). Guandalini [56] concluded that in UC, based on preliminary results, high-concentration probiotic formulations like the proprietary preparation VSL#3 could be effective as adjuvant therapy, both in inducing and maintaining remission. No general recommendation for the use of probiotics as adjuvant therapy in UC can be given until the results are confirmed by larger studies [20] and no proven benefit has yet been shown for probiotics in patients with CD [20, 56].

Prevention and Treatment of Allergies

Allergic responses during childhood most commonly occur as atopic dermatitis, eczema, wheezing, and asthma. According to the "hygiene hypothesis" atopic, T-helper cell (Th) type 2-mediated diseases are on the rise over the last decades at least in part due to decreased exposure to microbial antigens early in life, improved sanitation, and relative sterility of the modern environment. Decreased antigen exposure adversely affects the developing immune system and increases the prevalence of atopic disease [15, 58]. The intestinal mucosal immune system is important for the development of tolerance towards dietary and harmless microbial and environmental antigens. The normal interaction of infants with microbes is thought to be compromised in the Western world, with a reduction in

Bifidobacteria and an increase in *Clostridium* species, in particular in infants born by Cesarian section and/or fed with formula [57, 58]. The efficacy of probiotic prevention of allergic disease was shown in studies in which mothers with a history of allergy received LGG supplements during the last trimester of pregnancy and the breast-feeding period. Follow-up of children at 2, 4, and 7 years of age indicated lower prevalence and cumulative incidence of atopic dermatitis in children of so-treated mothers [59–61]. However, allergic rhinitis and asthma tended to be more common in the probiotic group.

A more recent study with *L. reuteri* failed to confirm that pre- and postnatal supplementation is effective in preventing atopic dermatitis, but showed an effect on IgE-associated eczema during the second year of life [62]. Supplementation of high-risk infants with *L. acidophilus* (LAVRI-A1) had no effect on atopic dermatitis at 12 months of age, but a higher risk of cow's milk sensitization was found in the supplemented group [63]. Therefore, the positive effect reported by Kalliomäki et al. [59, 61] might be related to the strain and/or the study design and needs further confirmation. A recent meta-analysis concluded that there is insufficient evidence to recommend single use of lactic acid bacteria for prevention of eczema [64].

Safety

In most safety studies selected probiotic strains were provided as supplements or fortified formula to premature and term infants, between 6 and 36 months of age. Several randomized clinical trials in healthy infants and toddlers indicate that *L. acidophilus* johnsonii La1 [65, 66], *L. rhamnosus* LPR (Chouraqui et al. [67]), LGG [68], *L. reuteri* ATCC 55730 [24], and *L. salivarius* CECT5713 [25] are safe. Some lactobacilli (e.g., *L. acidophilus* johnsonii La1) produce D-lactate, which was supposed to result in metabolic acidosis if accumulated in infants. We have shown that the concentrations of *L. acidophilus* johnsonii La1 in formulas for older infants and toddlers (10^7 to 10^8 CFU/g formula powder) do not cause any increase in urinary D-lactate excretion and therefore are safe for this age group [66]. However, concerns about safety of different Lactobacilli and Saccharomyces have been raised in high-risk groups after severe adverse events occurred [69]. Those groups would include premature and immunocompromised patients and/or patients having intravenous catheters or other indwelling devices. Due to the limited safety information Lactobacilli cannot be recommended in those children [20].

Bifidobacterium lactis given with or without Streptococcus thermophilus has a long history of safe use in children [21, 70]. A recent systematic review indicated *Bifidobacterium lactis* to be safe even in the most vulnerable group of infants—those born with birth weight <2,500 g and treated in intensive care units [46]. In developing countries, either no adverse reactions were reported in healthy [71] and HIV-infected children [72] receiving formulas supplemented with *Bifidobacterium lactis* in randomized clinical trials.

The use of prebiotic products such as follow-up formula, growing-up milks, and cereals after 6 months of age is considered to be safe [19, 20, 65, 73]. Two well-conducted systematic reviews of randomized clinical trials in healthy young infants confirm safety [74, 75]. The most commonly studied prebiotic were galactooligosaccharides (GOS) with or without fructooligosaccharides (FOS) [19]. One recent sufficiently powered randomized trial in children under mechanical ventilation confirmed safety of a mixture of probiotics (*Lactobacillus paracasei* NCC 246, *Bifidobacterium longum* NCC 3002) and prebiotics (FOS, Inulin, Acacia gum; [76]). More studies need to confirm safety of different prebiotic or synbiotic mixtures for high-risk children [19].

Conclusions and Recommendations

The use of pre- and probiotics to exert beneficial influence on the gut microbiota has shown great potential for the prevention and treatment of gastrointestinal symptoms and diseases. However, current evidence is yet insufficient to come up with general recommendations. Best evidence of efficacy exists for the treatment of acute infectious diarrhea with probiotics shown to reduce duration and stool frequency, although optimal probiotic strain and dosage for individual patient groups still remain to be determined. There is less, but consistent evidence for similar effects in persistent diarrhea in children. For the prevention of diarrhea in children for most probiotics only one positive study is available and data are too limited for conclusions. The same applies to prebiotics for which randomized clinical trials with outcomes relevant to diarrhea prevention and treatment as primary endpoint are lacking. Data on the efficacy of probiotics for the prevention of AAD are controversial but at least promising for the strains *B. lactis*/*S. thermophilus*, LGG, and *S. boulardii*. Regarding *Helicobacter pylori*, probiotics might be a useful adjunct treatment to antibiotics to foster eradication rates and alleviate side effects, particularly diarrhea, although this is not yet endorsed by official evidence-based guidelines. Available data is not conclusive regarding the efficacy of probiotics, neither in the prevention of H. pylori and of allergic diseases nor as adjuvant in the treatment of UC or CD. With the caveat that administration of life micro-organisms is never without risk and that safety data for some strains in high-risk groups is scarce, current probiotics can generally be considered safe.

References

1. Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science. 2010;328(5975):228–31.
2. Duncan SH, Lobley GE, Holtrop G, Ince J, Johnstone AM, Louis P, et al. Human colonic microbiota associated with diet, obesity and weight loss. Int J Obes (Lond). 2008;32(11):1720–4.
3. Wen L, Ley RE, Volchkov PY, Stranges PB, Avanesyan L, Stonebraker AC, et al. Innate immunity and intestinal microbiota in the development of type 1 diabetes. Nature. 2008;455(7216):1109–13.
4. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011;472(7341):57–63.
5. Food and Agriculture Organisation of the United Nations; World Health Organisation. Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. 2001. http://www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf. Accessed Dec 2011.
6. Food and Agriculture Organisation of the United Nations; World Health Organisation. Guidelines for the evaluation of probiotics in food: joint FAO/WHO Working Group report on drafting guidelines for the evaluation of probiotics in food. 2002. ftp://ftp.fao.org/es/esn/food/wgreport2.pdf Accessed Dec 2011.
7. Council for Agricultural Science and Technology. Probiotics: their potential to impact human health. Ames, IA: Council for Agricultural Science and Technology; 2007. http://www.cast-science.org/websiteUploads/publciation-PDFs/CAST%20Probiotics%20Issue%20Paper%20FINAL144.pdf. Accessed Dec 2011.
8. Ruemmele FM, Bier D, Marteau P, Rechkemmer G, Bourdet-Sicard R, Walker WA, et al. Clinical evidence for immunomodulatory effects of probiotic bacteria. J Pediatr Gastroenterol Nutr. 2009;48(2):126–41.
9. Bjorkstein B, Naaber P, Sepp E, Mikelsaar M. The intestinal microflora in allergic Estonian and Swedish 2-year-old children. Clin Exp Allergy. 1999;29(3):342–6.
10. Commane DM, Shortt CT, Silvi S, Cresci A, Hughes RM, Rowland IR. Effects of fermentation products of pro-and prebiotics on trans-epithelial electrical resistance in an in vitro model of the colon. Nutr Cancer. 2005;51(1):102–9.
11. Roberfroid M. Prebiotics; the concept revisited. J Nutr. 2007;137(3 suppl 2):830S–7.
12. Grönlund MM, Gueimonde M, Laitinen K, et al. Maternal breast-milk and intestinal bifidobacteria guide the compositional development of the Bifidobacterium microbiota in infants at risk of allergic disease. Clin Exp Allergy. 2007;37(12):1764–72.
13. Perez PF, Doré J, Leclerc M, Levenez F, Benyacoub J, Serrant P, et al. Bacterial imprinting of the neonatal immune system: lessons from maternal cells? Pediatrics. 2007;119(3):e724–32.

14. Díaz-Ropero MP, Martín R, Sierra S, Lara-Villoslada F, Rodríguez JM, Xaus J, et al. Two Lactobacillus strains, isolated from breast milk, differently modulate the immune response. J Appl Microbiol. 2007;102(2):337–43.
15. Kaplan JL, Shi HN, Walker WA. The role of microbes in developmental immunologic programming. Pediatr Res. 2011;69(6):465–72.
16. Fukushima Y, Kawata Y, Hara H, Terada A, Mitsuoka T. Effect of a probiotic formula on intestinal immunoglobulin A production in healthy children. Int J Food Microbiol. 1998;42(1–2):39–44.
17. Rautava S, Arvilommi H, Isolauri E. Specific probiotics in enhancing maturation of IgA responses in formula-fed infants. Pediatr Res. 2006;60(2):221–4.
18. Holscher HD, Czerkies LA, Cekola P, Litov R, Benbow M, Santema S, et al. Bifidobacterium lactis Bb12 enhances intestinal antibody response in formula-fed infants: a randomized, double-blind, controlled trial. J Parenter Enteral Nutr. 2012;36:106S–17.
19. Braegger C, Chmielewska A, Decsi T, Kolacek S, Mihatsch W, Moreno L, et al. Supplementation of infant formula with probiotics and/or prebiotics: a systematic review and comment by the ESPGHAN committee on nutrition. J Pediatr Gastroenterol Nutr. 2011;52(2):238–50.
20. Thomas DW, Greer FR; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Gastroenterology, Hepatology, and Nutrition. Probiotics and prebiotics in pediatrics. Pediatrics. 2010;126(6):1217–31.
21. Saavedra JM, Bauman NA, Oung I, Perman JA, Yolken RH. Feeding of Bifidobacterium bifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhoea and shedding of rotavirus. Lancet. 1994;344(8929):1046–9.
22. Chouraqui JP, Van Egroo LD, Fichot MC. Acidified milk formula supplemented with bifidobacterium lactis: impact on infant diarrhea in residential care settings. J Pediatr Gastroenterol Nutr. 2004;38(3):288–92.
23. Corrêa NB, Péret Filho LA, Penna FJ, Lima FM, Nicoli JR. A randomized formula controlled trial of Bifidobacterium lactis and Streptococcus thermophilus for prevention of antibiotic-associated diarrhea in infants. J Clin Gastroenterol. 2005;39(5):385–9.
24. Weizman Z, Asli G, Alsheikh A. Effect of a probiotic infant formula on infections in child care centers: comparison of two probiotic agents. Pediatrics. 2005;115(1):5–9.
25. Maldonado J, Lara-Villoslada F, Sierra S, Sempere L, Gómez M, Rodriguez JM, et al. Safety and tolerance of the human milk probiotic strain Lactobacillus salivarius CECT5713 in 6-month-old children. Nutrition. 2010;26(11–12):1082–7.
26. Pedone CA, Arnaud CC, Postaire ER, Bouley CF, Reinert P. Multicentric study of the effect of milk fermented by Lactobacillus casei on the incidence of diarrhea. Int J Clin Pract. 2000;54(9):568–71.
27. Szajewska H, Kotowska M, Mrukowicz JZ, Armańska M, Mikołajczyk W. Efficacy of Lactobacillus GG in prevention of nosocomial diarrhea in infants. J Pediatr. 2001;138(3):361–5.
28. Guandalini S, Pensabene L, Zikri MA, Dias JA, Casali LG, Hoekstra H, et al. Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea: a multicenter European trial. J Pediatr Gastroenterol Nutr. 2000;30(1):54–60.
29. Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. Cochrane Database Syst Rev. 2010;11:CD003048.
30. Shornikova AV, Casas IA, Isolauri E, Mykkänen H, Vesikari T. Lactobacillus reuteri as a therapeutic agent in acute diarrhea in young children. J Pediatr Gastroenterol Nutr. 1997;24(4):399–404.
31. Shornikova AV, Casas IA, Mykkänen H, Salo E, Vesikari T. Bacteriotherapy with Lactobacillus reuteri in rotavirus gastroenteritis. Pediatr Infect Dis J. 1997;16(12):1103–7.
32. Eom TH, Oh EY, Kim YH, Lee HS, Jang PS, Kim DU, Kim JT, Lee BC. The therapeutic effects of *Lactobacillus reuteri* in acute diarrhea in infants and toddlers. Korean J Ped. 2005;48:986–90.
33. Bernaola Aponte G, Bada Mancilla CA, Carreazo Pariasca NY, Rojas Galarza RA. Probiotics for treating persistent diarrhoea in children. Cochrane Database Syst Rev. 2010;11:CD007401.
34. Brown KH, Perez F, Peerson JM, Fadel J, Brunsgaard G, Ostrom KM, et al. Effect of dietary fiber (soy polysaccharide) on the severity, duration, and nutritional outcome of acute, watery diarrhea in children. Pediatrics. 1993;92(2):241–7.
35. Moore N, Chao C, Yang LP, Storm H, Oliva-Hemker M, Saavedra JM. Effects of fructo-oligosaccharide-supplemented infant cereal: a double-blind, randomized trial. Br J Nutr. 2003;90(3):581–7.
36. Arslanoglu S, Moro GE, Boehm G. Early supplementation of prebiotic oligosaccharides protects formula-fed infants against infections during the first 6 months of life. J Nutr. 2007;137(11):2420–4.
37. Arslanoglu S, Moro GE, Schmitt J, Tandoi L, Rizzardi S, Boehm G. Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. J Nutr. 2008;138(6):1091–5.
38. Moro G, Arslanoglu S, Stahl B, Jelinek J, Wahn U, Boehm G. A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. Arch Dis Child. 2006;91(10):814–9.

39. Vandenplas Y, Veereman-Wauters G, De Greef E, Peeters S, Casteels A, Mahler T, et al. Probiotics and prebiotics in prevention and treatment of diseases in infants and children. J Pediatr (Rio J). 2011;87(4):292–300.
40. Szajewska H, Ruszczyński M, Radzikowski A. Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials. J Pediatr. 2006;149(3):367–72.
41. Johnston BC, Supina AL, Ospina M, Vohra S. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database Syst Rev. 2007;2:CD004827.
42. Kale-Pradhan PB, Jassal HK, Wilhelm SM. Role of Lactobacillus in the prevention of antibiotic-associated diarrhea: a meta-analysis. Pharmacotherapy. 2010;30(2):119–26.
43. Bergonzelli GE, Blum S, Brussow H, Corthésy-Theulaz I. Probiotics as a treatment strategy for gastrointestinal diseases? Digestion. 2005;72(1):57–68.
44. Felley CP, Corthésy-Theulaz I, Rivero JL, Sipponen P, Kaufmann M, Bauerfeind P, et al. Favourable effect of an acidified milk (LC-1) on Helicobacter pylori gastritis in man. Eur J Gastroenterol Hepatol. 2001;13(1):25–9.
45. Lesbros-Pantoflickova D, Corthésy-Theulaz I, Blum AL. Helicobacter pylori and probiotics. J Nutr. 2007;137(3 Suppl 2):812S–8.
46. Szajewska H, Horvath A, Piwowarczyk A. Meta-analysis: the effects of Saccharomyces boulardii supplementation on Helicobacter pylori eradication rates and side effects during treatment. Aliment Pharmacol Ther. 2010;32(9):1069–79. doi:10.1111/j.1365-2036.2010.04457.x. Epub 2010 Sep 16.
47. Koletzko S, Jones NL, Goodman KJ, Gold B, Rowland M, Cadranel S, et al. Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. J Pediatr Gastroenterol Nutr. 2011;53(2):230–43.
48. Day AS, Whitten KE, Bohane TD. Use of complementary and alternative medicines by children and adolescents with inflammatory bowel disease. J Paediatr Child Health. 2004;40(12):681–4.
49. Heuschkel R, Afzal N, Wuerth A, Zurakowski D, Leichtner A, Kemper K, et al. Complementary medicine use in children and young adults with inflammatory bowel disease. Am J Gastroenterol. 2002;97(2):382–8.
50. Mallon P, McKay D, Kirk S, Gardiner K. Probiotics for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2007;4:CD005573.
51. Gionchetti P, Rizzello F, Helwig U, Venturi A, Lammers KM, Brigidi P, et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. Gastroenterology. 2003;124(5):1202–9.
52. Mimura T, Rizzello F, Helwig U, Poggioli G, Schreiber S, Talbot IC, et al. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. Gut. 2004;53(1):108–14.
53. Kuisma J, Mentula S, Jarvinen H, Kahri A, Saxelin M, Farkkila M. Effect of Lactobacillus rhamnosus GG on ileal pouch inflammation and microbial flora. Aliment Pharmacol Ther. 2003;17(4):509–15.
54. Elahi B, Nikfar S, Derakhshani S, Vafaie M, Abdollahi M. On the benefit of probiotics in the management of pouchitis in patients underwent ileal pouch anal anastomosis: a meta-analysis of controlled clinical trials. Dig Dis Sci. 2008;53(5):1278–84.
55. Miele E, Pascarella F, Giannetti E, Quaglietta L, Baldassano RN, Staiano A. Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. Am J Gastroenterol. 2009;104(2):437–43.
56. Guandalini S. Update on the role of probiotics in the therapy of pediatric inflammatory bowel disease. Expert Rev Clin Immunol. 2010;6(1):47–54.
57. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med. 2002;347(12):911–20.
58. van Nimwegen FA, Penders J, Stobberingh EE, Postma DS, Koppelman GH, Kerkhof M, et al. Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. J Allergy Clin Immunol. 2011;128(5):948–55.
59. Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet. 2001;357(9262):1076–9.
60. Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet. 2003;361(9372):1869–71.
61. Kalliomäki M, Salminen S, Poussa T, Isolauri E. Probiotics during the first 7 years of life: a cumulative risk reduction of eczema in a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2007;119(4):1019–21.
62. Abrahamsson TR, Jakobsson T, Böttcher MF, Fredrikson M, Jenmalm MC, Björkstén B, et al. Probiotics in prevention of IgE-associated eczema: a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol. 2007;119(5):1174–80.
63. Taylor AL, Dunstan JA, Prescott SL. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. J Allergy Clin Immunol. 2007;119(1):184–91.
64. Zhu DL, Yang WX, Yang HM. Meta analysis of lactic acid bacteria as probiotics for the primary prevention of infantile eczema. Zhongguo Dang Dai Er Ke Za Zhi. 2010;12(9):734–9.

65. Brunser O, Figueroa G, Gotteland M, Haschke-Becher E, Magliola C, Rochat F, et al. Effects of probiotic or prebiotic supplemented milk formulas on fecal microbiota composition of infants. Asia Pac J Clin Nutr. 2006;15(3):368–76.
66. Haschke-Becher E, Brunser O, Cruchet S, Gotteland M, Haschke F, Bachmann C. Urinary D-lactate excretion in infants receiving Lactobacillus johnsonii with formula. Ann Nutr Metab. 2008;53(3–4):240–4.
67. Chouraqui JP, Grathwohl D, Labaune JM, Hascoet JM, de Montgolfier I, Leclaire M, et al. Assessment of the safety, tolerance, and protective effect against diarrhea of infant formulas containing mixtures of probiotics or probiotics and prebiotics in a randomized controlled trial. Am J Clin Nutr. 2008;87(5):1365–73.
68. Vendt N, Grünberg H, Tuure T, Malminiemi O, Wuolijoki E, Tillmann V, et al. Growth during the first 6 months of life in infants using formula enriched with Lactobacillus rhamnosus GG: double-blind, randomized trial. J Hum Nutr Diet. 2006;19(1):51–8.
69. Boyle RJ, Robins-Browne RM, Tang ML. Probiotic use in clinical practice: what are the risks? Am J Clin Nutr. 2006;83(6):1256–64; quiz 1446–7.
70. Saavedra JM, Abi-Hanna A, Moore N, Yolken RH. Long-term consumption of infant formulas containing live probiotic bacteria: tolerance and safety. Am J Clin Nutr. 2004;79(2):261–7.
71. Nopchinda S, Varavithya W, Phuapradit P, Sangchai R, Suthutvoravut U, Chantraruksa V, et al. Effect of bifidobacterium Bb12 with or without Streptococcus thermophilus supplemented formula on nutritional status. J Med Assoc Thai. 2002;85 Suppl 4:S1225–31.
72. Velaphi SC, Cooper PA, Bolton KD, Mokhachane M, Mphahlele RM, Beckh-Arnold E, et al. Growth and metabolism of infants born to women infected with human immunodeficiency virus and fed acidified whey-adapted starter formulas. Nutrition. 2008;24(3):203–11.
73. Brunser O, Gotteland M, Cruchet S, Figueroa G, Garrido D, Steenhout P. Effect of a milk formula with prebiotics on the intestinal microbiota of infants after an antibiotic treatment. Pediatr Res. 2006;59(3):451–6.
74. Rao S, Srinivasjois R, Patole S. Prebiotic supplementation in full-term neonates: a systematic review of randomized controlled trials. Arch Pediatr Adolesc Med. 2009;163(8):755–64.
75. Osborn DA, Sinn JK. Prebiotics in infants for prevention of allergic disease and food hypersensitivity. Cochrane Database Syst Rev. 2007;4:CD006474.
76. Simakachorn N, Bibiloni R, Yimyaem P, Tongpenyai Y, Varavithaya W, Grathwohl D, et al. Tolerance, safety, and effect on the faecal microbiota of an enteral formula supplemented with pre- and probiotics in critically ill children. J Pediatr Gastroenterol Nutr. 2011;53(2):174–81.

Chapter 22
Prebiotics and Probiotics: Infant Health and Growth

Flavia Indrio and Giuseppe Riezzo

Key points

- The adequate establishment of the intestinal flora after birth plays a crucial role in the development of gut barrier function, the innate and adaptive immune system, and GI motility to prevent the expression of clinical gastrointestinal disease states.
- Taking breast feeding as the natural example of functional food able to induce effects beyond nutritional needs, the prebiotic/probiotic formula should be considered as a physiological approach to influence intestinal microbiota early in the life and so the related intestinal functions.
- Bifidobacteria and lactobacilli are the most popular micro-organisms for probiotic applications and the most effective ones are of human origin. There are several reports of probiotics and prebiotics in disease prevention or enhancement of immune function, reinforcement of the gut defense, and maturation of gastrointestinal motility.
- Most of the studies to date using probiotics and prebiotics to manipulate the intestinal microbiota and to prevent or treat disease have been empiric and much more needs to be learned about the indigenous flora and their interactions with the developing intestinal tract before we can be comfortable in routinely manipulating the intestinal microbial ecosystem.

Keywords Newborns • Prebiotics • Probiotics • Breast milk • Formula • Nutrition • Motility • Gastric emptying • Intestinal immunity

Introduction

Human breast milk is always seen as the preferred choice for infant nutrition [1]. It is a wholly nutritious complete food for infants and contains many components that have important bioactive roles [2, 3]. In particular, several glycoprotein and soluble oligasaccharides were found to be selectively stimulatory for bifidobacteria [4, 5]. Gut flora dominated by bifidobacteria account for healthier

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outcome of breast-milk infants respect to formula-fed ones. Some kinds of oligosaccharides act as soluble receptors of different pathogens at mucosal level, so demonstrating a higher immunological resistance in breast-milk infants [6].

During the last few years the role of the intestinal microflora in health and disease has become increasingly recognized and diet has been demonstrated to influence the relative amount of microbial species and strains of the gastrointestinal tract [7]. Much interest exists in modulating the composition of the gut towards a potentially more beneficial community. This outcome may be achieved by using targeted dietary supplementation [8]. Whenever breast feeding is not possible or not chosen, infant formulas are the alternatives. One approach to fortify the biological role of formula feeds has been to use probiotics and prebiotics as constituents [9].

Bifidobacteria and lactobacilli are the most popular micro-organism for probiotic applications and the most effective ones are of human origin [10]. Probiotic supplementation in infant formulas has shown that some strains may persist in the infant gut [11, 12] and lower stool pH [13]. Supplementation with LGG [14] and with Bifidobacteriumbifidum and Streptococcus thermophilus has been successful in preventing viral diarrhea in infants [15]. An alternative approach for intestinal flora modulation is the use of prebiotics, nondigestible food component that selectively stimulate certain bacteria resident in the gut [16] rather than introducing exogenous species, as is the case with probiotics. Any dietary component that reaches the colon intact is a potential prebiotic but most of the interest in the development of prebiotics is aimed at nondigestible oligosaccharides. The prebiotic approach has the advantage that heat stability or exposure to O_2 is not an issue and it is concentrated towards stimulation or enhancement of the indigenous probiotic flora. Hence, for practical as well as ethical reasons their use in formula feeds currently seems to be more widespread than the use of probiotics. The targeted health benefits are similar. It is likely that inclusion of such dietary prebiotic components in moderate amounts may benefit formula-fed infants by establishing an intestinal flora with more bifidobacteria and less harmful bacteria. The health aspects of this approach have not yet been determined.

A further possibility in microflora management is the use of synbiotics, the combination of probiotics and prebiotics. A synbiotic has been defined as ‘a mixture of probiotics and prebiotics’ that beneficially affects the host by improving the survival and implantation of live microbial dietary supplements in the GI tract, by selectively stimulating the growth and/or activating the metabolism of one or a limited number of health-promoting bacteria, and thus improving host welfare. However, they have not yet entered the infant food market.

The Microbiome–Host Cross-Talking

The work of Pasteur, Lister, and Koch demonstrated that microbes play a significant role in the cause and prevention of human disease. It is now known that bacteria are both helpful and harmful to their human hosts. The human microbiome, broadly defined, is the full collection of microbes (bacteria, fungi, viruses, etc.) and their DNA that naturally exist in a given habitat of the human body [17]. The habitat with the largest and most complex arrangement of microorganisms is the gastrointestinal system, which includes approximately one trillion (10^{12}) bacterial cells per 1 g of feces in the average human individual [18]. The collective bacterial genome of the human microbiota encodes an estimated two to four million genes, surpassing the human genome by a staggering 140-fold. Intestinal bacteria carry thousands of enzymatic reactions, such as synthesis of vitamins, harvest of otherwise inaccessible nutrients, regulation of drug metabolism, renewal of gut epithelial cells, and development and activity of the immune system and thus act as an “organ within an organ.” It is the variability between harmful and helpful bacteria that dictates health or disease. The variation in a specific microbiome may result from a combination of factors such as host genotype, host physiology, host immune system (including the properties of the innate and adaptive immune systems), host lifestyle (including diet), host pathobiology (disease status), host environment, and the presence of transient populations

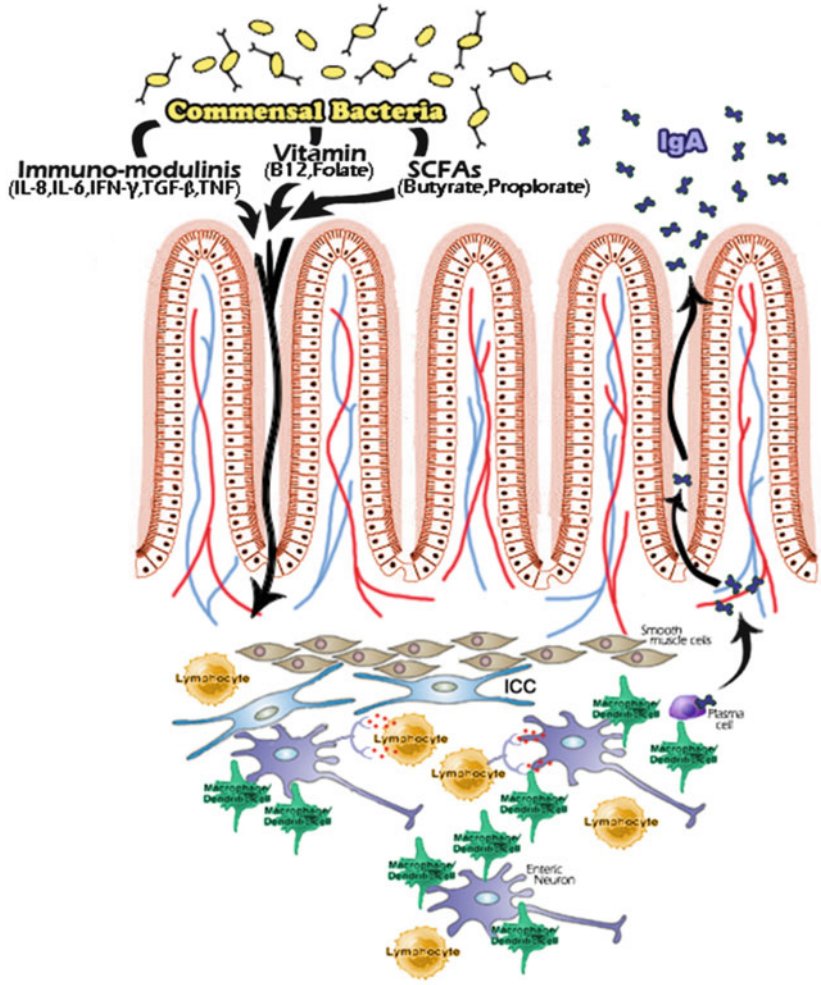

Fig. 22.1 Commensal bacteria inhabiting the human intestine (i.e., intestinal microflora) participate in the development and maintenance of gut sensory and motor functions, including the promotion of intestinal propulsive activity. The normal intestinal motility requires the coordination between enteric motor neurons ICC and smooth muscle cells. The ENS influence the gut directly with the activity related to the contraction (SMC ICC) and indirectly influencing the cells of the gut immune system. The functional bidirectional interaction acts via neuroimmune peptide receptor on immune cells and on several receptor for immune mediators expressed on enteric nerves. Immune cells release mediators (cytokines, prostanoids) in response to neural stimuli. Enteric and sensory nerves respond to immune stimuli

of microorganisms. Building on this work, the aim of contemporary scientists has been to develop a more precise understanding of the mechanisms of action between microbes and gastrointestinal tract [19] (Fig. 22.1).

The intestinal tract is no more considered as a simple tube that provide the progression and digestion of food but a dynamic interface between the external environment and the mammalian host. Such function is performed by the selective regulation of cells, microorganisms, and macromolecules trafficking between the intestinal lumen and the submucosa. This function requires sophisticated sensor systems to be responsive to a wide variety of stimuli and to modulate proper set of responses to the complex climax community of microbial partners that populate the GI tract. What is becoming increasingly clear is that some microorganisms have developed tools to twist the host–microbial

interaction to their own advantage, so triggering host pathophysiological changes leading to local and even systemic disorders. As a result, new knowledge about specific factors that play a role in the complex relationships between bacterial cells and gastrointestinal tract has been developed. The most important mechanisms involved are briefly reported below.

Intestinal Barrier Function

The intact intestinal epithelium with the normal intestinal microflora represents a stable barrier for protecting the host and providing normal intestinal function. In fact, the gut barrier is able to prevent luminal pathogens and harmful substances from entering into the internal milieu and yet promoting digestion and different architectural units of this barrier. Exposed to trillions of luminal microbes, the intestinal mucosa averts threats by signaling to the innate immune system, through pattern recognition receptors, to respond to the commensal bacteria by developing tolerance towards them [20]. This system also acts by protecting against pathogens by elaborating and releasing protective peptides, cytokines, chemokines, and phagocytic cells. The intestinal mucosa is constantly sampling luminal contents and making molecular adjustments at its frontier. When either the normal microflora or the epithelial cells are disturbed by triggers such as dietary antigens, pathogens, chemicals, or radiation, defects in the barrier mechanisms become evident. Altered permeability further facilitates the invasion of pathogens, foreign antigens, and other harmful substances [21]. Disturbed intestinal microflora may lead to diarrhea, mucosal inflammation, or activation of harmful drugs and carcinogens in intestinal contents [22].

GI Mucosal Immunology

Gut associated lymphoid tissue (GALT) is composed of both inductive (Peyer's patches) and effector sites (intraepithelial cells and lamina propria). GALT, dealing with intestinal microflora, prevents potentially harmful intestinal antigens from reaching the systemic circulation and induces systemic tolerance against luminal antigens by a process that involves polymeric immunoglobulin A (IgA) secretion and the induction of regulatory T cells [23]. The precursors of IgA plasma cells are generated in follicular organized structures with the help of T cells and the secreted IgAs provide protection against mucosal pathogens. However, only recently we began to appreciate that IgAs play key roles in regulation of bacterial communities in the intestine and that the repertoire of gut microbiota is closely linked to the proper functioning of the immune system [24, 25].

Antigen-presenting cells (APC) (macrophages, dendritic cells, B cells) efficiently take up and transport a variety of microorganisms and present antigen therefore, isolated lymphoid follicles are proposed to be local sites for lymphocytic, antigen, and antigen-presenting cell interactions. In addition to macrophages, dendritic cells also capture antigens present in the intestinal lumen by sending dendrites through tight junctions between epithelial cells while maintaining barrier integrity and then rapidly migrating to other areas, such as mesenteric lymphonodes. Recognition of antigens by dendritic cells triggers a family pattern of recognition receptor (TLRs) which change cell phenotype and function. In intestinal epithelial cells, TLRs play a role in normal mucosal homeostasis and are particularly important in the interaction between the mucosa and the luminal flora. TLRs direct immune responses by activating signaling events leading to elevated expression of factors, such as cytokines and chemokines that recruit and regulate the immune and inflammatory cells, which then either initiate or enhance host immune responses [26].

The Enteric Nervous System and Gastrointestinal Motility

Brain–intestinal interactions are well-known mechanisms for the regulation of intestinal function in both healthy and diseased states. A role of the enteric microbes in these interactions has only been recognized in the past few years. The brain can influence commensal organisms via changes in gastrointestinal motility, secretion, and intestinal permeability, or directly, via signaling molecules released into the gut lumen from cells in the lamina propria (enterochromaffin cells, neurons, immune cells) [27]. Enteric microbiota communication occurs via epithelial-cell, receptor-mediated signaling and, when intestinal permeability is increased, through direct stimulation of host cells in the lamina propria. Integral to these communications are enterochromaffin cells, which serve as bidirectional transducers that regulate communication between the intestinal lumen and the nervous system [28]. Disruption of the bidirectional interactions between the enteric microbiota and the nervous system may be involved in the pathophysiology of acute and chronic gastrointestinal disease states, including functional and inflammatory bowel disorders [29].

Normal intestinal motility requires the coordination between the extrinsic neurons, enteric motor neurons, interstitial cells of Cajal (ICC), and smooth muscle cells. The enteric nervous system (ENS) is a complex integrative brain (also called the second brain) which is capable of controlling the gastrointestinal function. The ENS influences the gut directly with the activity related to the contraction and indirectly influencing the cells of the gut immune system and the epithelial cells. This interaction is bidirectional and relies on the mechanisms of neuroimmune interaction, which involves bacterial component activation of Toll-like and other bacterial molecular pattern receptors to trigger innate immune responses and the intestinal neural pathways [30].

The Perinatal and Neonatal Challenge

Perinatal and neonatal health and growth represents areas of high importance for this new knowledge and an intense area of research because the human microbiome is significantly influenced during pregnancy, birth, and the neonatal period [31, 32]. The newborn infant leaves a germ-free intrauterine environment to enter a contaminated extrauterine world and must have adequate intestinal defenses to prevent the expression of clinical gastrointestinal disease states [33]. The adequate establishment of the intestinal flora after birth plays a crucial role in the development of gut barrier function, the innate and adaptative immune system, and GI motility [34].

When the fetus is born via the vaginal canal, the bacterial exposure is representative of the microbes present in the mother's vagina. When the fetus is born via cesarean section, the intestinal microbiome lack any bacteria representative of the vaginal canal and the bacterial exposure is representative of the mother's skin [35]. The result of this difference is that infants born vaginally acquire bacterial species including Lactobacillus, Prevotella, and Sneathia, and infants born by cesarean section obtain Staphylococcus, Corynebacterium, and Propionibacterium. The differences in these exposures are significant. Not only are the functionalities of the bacterial species specific to the vagina and skin unique, but also of great importance, as the direct transmission of vaginal microbiota during birth represents an important defense mechanism.

Full-term newborns have a fully developed intestinal mucosal immune system, but the actual protective function of the gut requires the microbial stimulation of initial bacterial colonization. The gut interacts with intestinal bacteria, both resident and ingested, to develop protective mechanisms (via improving gut barrier function and immune stimulation for defense) and appropriate, nonexaggerated responses (via immune modulation and immune tolerance) to support host health. The mechanisms of this interaction between host and bacteria are increasingly being unraveled and in great part

Table 22.1 Digestion, absorption, and motility in relation to preterm conditions

	Very preterm newborns										Preterm newborns				Full-term newborns					
Gestational week	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
Digestion	Progressive detecting of sucrose, lactase, and GI hormones and peptides →										Sucrase 70% of adult ↓						Lactase peak ↓			
Absorption	Glucose transporter presence →																			
	Gastric lipase increase →																			
Motility	Swallowing present →																			
	Disorganized motility →					Fetal mot →							MMC →				Mature motility →			
% survival	17	39	50	80	90	90	90	90	90	95	as full term	as full term	as full term	as full term	as full term	as full term	as full term	as full term	as full term	as full term

explain the clinical benefits that have been reported with specific probiotic bacteria by enhancing host defense mechanisms. For example, commensal bacteria can stimulate the synthesis and secretion of polymeric IgA as reported earlier and help to produce a balanced T helper cell response and prevent an imbalance contributing in part to clinical disease (Th2 imbalance contributes to atopic disease [36] and Th1 imbalance contributes to inflammatory chronic diseases [37]). Furthermore, a series of pattern recognition receptors, toll-like receptors on gut lymphoid and epithelial cells that interact with bacterial molecular patterns (e.g., endotoxin, lipopolysaccharide, flagellin, etc.), help modulate intestinal innate and adaptive immune response.

Premature infants have an abnormal colonization, tend to colonize with fewer bacteria, are routinely administered antibiotics, are often born via caesarian section, and are exposed to highly pathogenic institutional organisms [38, 39]. Premature infants frequently have intestinal motor and immunological immaturity that contributes to feeding intolerance. Thus, examining the intestinal bacteria present in premature infants may be an important determinant in the pathogenesis of disease, specifically inflammatory gastrointestinal disease such as necrotizing enterocolitis (NEC) [40]. Using advanced technologies and stool samples, studies have shown that infants who develop NEC have significantly less bacterial diversity in their intestinal microbiome [41]. The limited diversity identified in these infants is an important finding; it adds evidence to the evolving notion that NEC, like many diseases, is not caused by a single bacterial organism but the presence of certain pathogenic bacteria and the lack of protective bacteria [42].

A close association exists between epitheliahomeostasis and the absorptive function of the intestine. In addition, luminal nutrients are absolutely essential for intestinal development during the postnatal period. The transport of solute is not constant. Alterations in cell proliferation, the migration of enterocytes, a change in mucosal surface area, membrane fluidity, or paracellular permeability can alter the function of the intestine. A functionally insufficient intestine is unable to hydrolyze and absorb milk. This inefficiency alters other intestinal functions such as motor activity [43] and hormone secretions [44]. Therefore, the digestion and absorptive capacity are enhanced during development to support both intestinal and full body growth. The close relationship of the resident intestinal microbes to neural, immunological, and muscular processes such as intestinal motility and neurodevelopment is also being suggested.

There is little data available about the development of the motility function and of the mucosal barrier of the human gut, and in particular about the motility patterns and mucosal changes in newborns during early days of life (Table 22.1). Suck and swallow coordination is often poor before 34

weeks' gestation. Intestinal motility is fundamental for proper absorption, digestion, and movement of nutrients down in the GI tract. The fetal pattern of intestinal motility presents four specific stages according to gestational age: disorganized motility from 25 to 30 weeks, the fetal complex from 30 to 33 weeks, propagation of migrating motor complex (MMC) from 33 to 36 weeks, and mature interdigestive motility from 36 weeks to term [45]. Amplitude of motor activity, time of quiescent, antroduodenal coordination, number of cluster, and propulsive activity all increase with gestational age. A term infant exhibits the necessary GI structural and functional characteristics for the assimilation of the nutrient in colostrum and breast milk. Term infants are able to consume nutrients in adequate quantities to promote a rapid growth after birth. The majority of late preterm newborns are able to tolerate human milk and formula without difficulty despite underdeveloped swallowing reflex, reduced lactase enzyme activity, and immature motility pattern for digestion. However, feeding intolerance is a recurrent problem in the clinical care of preterm infants and occurs mainly in the first week of life, suggesting the presence of a maturation pattern of gastrointestinal tract [46]. It is known that functional maturation of the gastrointestinal tract is quite different over time with respect to its anatomical development [47, 48]. Intestinal dysmotility is typically present up to 34 weeks' gestation but may persist in some late preterm infants. Some infants may require a longer-than-normal interval between feedings because of a delay in motility and gastric emptying. Besides, intestinal musculature is affected by the introduction of early enteral feeding. There are reports that motor responses resemble more mature interdigestive and postprandial patterns in preterm infants fed partial enteral vs. parenteral nutrition [49]. Nutrients are required in order to improve motor activity to obtain a more rapid transition to fully enteral feeding since nutrients interact with gut flora and epithelium in a complex manner behind the energy needs. The modulation of gastrointestinal motility, along with the microbiota–immune system modulation could be considered important factors in formulating the best possible nutrition for premature newborns as will be described in the next section.

Enriched Formulas: The Probiotic and Prebiotic Paradigm

Breast feeding constitutes the ideal food for newborns because it provides molecules with antimicrobial activity [50] as well some strains of probiotic bacteria [51] which influence intestinal microbiota [52]. Breast milk contains prebiotic oligosaccharides, like inulin-type fructans, which are not digested in the small intestine but enter the colon as intact large carbohydrates that are then fermented by the resident bacteria to produce short chain fatty acids (SCFA). The nature of this fermentation and the consequent pH of the intestinal contents dictate proliferation of specific resident bacteria. For example, breast milk-fed infants with prebiotics present in breast milk produce an increased proliferation of bifidobacteria and lactobacilli (probiotics), whereas formula-fed infants produce more enterococci and enterobacteria. Animal and clinical studies have shown that inulin-type fructans will stimulate an increase in commensal bacteria and these bacteria have been shown to modulate the development and persistence of appropriate mucosal immune responses [53]. Moreover, the breast milk induces optimal gastrointestinal motility pattern inducing relaxation of the proximal stomach, lower esophageal sphincter, and reducing gastric emptying [54, 55].

Taking breast feeding as the natural example of infant nutrition, the prebiotic/probiotic approach should be considered as a physiological approach to influence intestinal microbiota early in the life as reported in the previous paragraphs. Probiotics have been used for many years in the animal fed industry, but they are now increasingly made available in many forms and can be purchased over the counter as freed-dried preparations in health food stores. Thus, possible health benefits associated with the administration of probiotic organisms are widely gaining acceptance. For example, there are several reports of disease prevention or enhancement of immune function resulting in the prevention of allergic diseases and reinforcement of the gut defense [56] and treatment of chronic inflammatory diseases

in children [57]. Furthermore, these organisms are thought to prevent the attachment of pathogens to enterocytes and invasion of these cells [58]. Bacterial translocation from the gastrointestinal tract is an important pathway initiating late-onset sepsis and NEC in very low-birth-weight infants. The emerging intestinal microbiota, nascent intestinal epithelia, naive immunity, and suboptimal nutrition (lack of breast milk) have roles in facilitating bacterial translocation. Feeding lactoferrin, probiotics, or prebiotics has presented exciting possibilities to prevent bacterial translocation in preterm infants, and clinical trials will identify the most safe and efficacious prevention and treatment strategies [59]. Furthermore, probiotic bacteria have been shown to enhance the human intestinal epithelial barrier function [60] so explain another way to prevent the translocation of potentially harmful organisms. Last, some strains of probiotic bacteria induce the production of the antimicrobial peptide human beta-defensin by the epithelium and immune cells, peptides that have been recognized to play a key role in the host defense against infection. This data indicates both a direct and indirect mechanisms of controlling potentially harmful bacteria by probiotics [61].

Prebiotics can simulate the bifidogenic effects of breast milk oligosaccharides and have been shown to exert long-term effects (up to 2 years) for protecting against infection, lowering the incidence of allergy, and also exerting positive consequences for the postnatal development of the immune system [62]. For example, primary prevention trials in infants have provided promising data on prevention of infections and atopic dermatitis [63]. Prebiotic seems to play via the activation of a human antimicrobal protein, the cathelicidin by means of butyrate [64]. Butyrate is a by-product of bacterial fiber fermentation that is produced by endogenous intestinal flora, and it is the major trophic factor for colonocytes. A recent compelling study showed that oral butyrate treatment of Shigella-infected dysenteric rabbits led to improvement of clinical symptoms, decreased blood in the stool, and a reduction in the bacterial load in the stool [65]. These data not only support the notion that cathelicidin is an essential effector molecule but also suggest that certain intestinal infections may be treatable through stimulation of epithelium-derived antibiotics. Additional well-designed prospective clinical trials and mechanistic studies are needed to advance knowledge further in this promising field.

The addition of prebiotic and probiotic to a formula induces a GI motility pattern similar to that one induced by breast milk. Oral probiotic supplementation in preterm newborns improves feeding tolerance, reduces the crying time, and increases stool frequency. Concerning physiological parameters, the newborns fed with formula added with probiotics show a faster gastric emptying rate and smaller fasting antral area. Safety and tolerance of a probiotic formula with Lactobacillus reuteri was recently described in full-term infants [66]. The action of probiotic on upper gastrointestinal motility could be explained in several ways. Volume and chemical characteristics of meals in the gut have been supposed to induce vagal signal affecting gastric emptying [67]. The fiber content was associated with a significant increase in gastric antrum motility respect to other diets [68]. Bacteria metabolites such as SCFA may stimulate smooth muscle [69]. In the colon they inhibit peristaltic activity and may stimulate tonic activity. Last, SCFA modify upper motility, inducing relaxation of the proximal stomach, lower esophageal sphincter, and reducing gastric emptying via the involving of GI hormones as polypeptide YY [70, 71]. Crosstalk between the digestive nervous and motor activities, immune-related mechanisms, and probiotics has become the main physiologic mechanism involved. No data are available concerning the role of the SCFA in preterm newborns, but the mechanism of probiotics on the gastric emptying may be the same as in adults.

There are a lot of study concerning gastric motility and emptying in preterm and term newborns in relation to gastrointestinal function as feeding tolerance and regurgitation. As regard gastric emptying time, a smaller fasting antral area was found in preterm fed with formula added with *L reuteri* compared to that one fed with formula with placebo and newborns fed with breast milk. Furthermore, the gastric emptying rate was significantly faster in formula added with probiotics group respect to breast milk and formula plus placebo (Fig. 22.2). All these findings could be markers of a reduced gastric residual in newborns fed with probiotics respect to formula-fed newborns. The clinical coun-

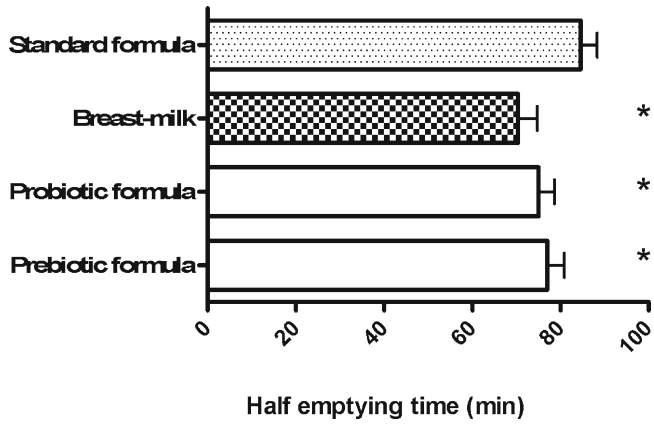

Fig. 22.2 The half emptying times recorded after 30 days treatment is reported. A clear difference in the half emptying time was evident between the study groups and placebo formula group. Data are expressed as Mean ± SD. Data analysis: ANOVA on ranks $p = 0.005$; post hoc test Dunn's test vs. control: prebiotic, probiotic formula and breast-milk vs. placebo formula $p < 0.05$. *GE* gastric emptying

terpart of this physiological condition may be the reduced numbers of regurgitation. Actually a recent work on infants with cow's milk allergy reports a close link between vomiting, gastro-esophageal reflux, and gastric emptying time [72].

The action of prebiotic on upper gastrointestinal motility might be explained by several physiological pathways. The most important mechanism seems to be the same as the probiotic pathway and was described above as interaction between colonic SCFAs and the polypeptide YY (Fig. 22.2). A faster gastric emptying in preterm infants can lead to luminal nutrients remaining in the intestine shorter and prevent the inflammation cascade and reduce the development of NEC [73]. It has been suggested a role of pre- and probiotic in such infectious disease. Postinfectious enteric muscle dysfunction, the state of persistent dysfunction of the neuromuscular tissues maintained by the production of mediators such as TGF beta and prostaglandin E2 by intestinal muscle layers themselves [74] seems to be involved. The ICC network, the pacemaker of GI electrical activity, also could be damaged by inflammation and such alteration may explain motor abnormality as supported by Wang et al. [75]. Probiotics can restore muscle function after GI infection modulate the mechanisms affecting multiple proteins and other components of excitation–contraction coupling [76].

Conclusion

The intestine serves as a vast interface between our internal and external environments. Evidence is rapidly accumulating that the microbes residing within the intestinal tract play major roles in the development of the immune system and interact with the intestinal as well as central nervous systems. The implications of these interactions in health and disease are becoming increasingly evident and in some cases manipulations of the microbial ecosystems suggest significant benefit. Most of the studies to date using probiotics and prebiotics to manipulate the intestinal microbiota and to prevent or treat disease have been empiric and much more needs to be learned about the indigenous flora and their interactions with the developing intestinal tract before we can be comfortable in routinely manipulating the intestinal microbial ecosystem.

References

1. Cuthbertson WJF. Evolution of infant nutrition. Br J Nutr. 1999;81:359–71.
2. Goldman AS, Chheda S, Garofalo R. Spectrum of immunomodulating agents in human milk. Int J Pediatr Hematol Oncol. 1997;4:491–7.
3. Garofalo RP, Goldman AS. Expression of functional immunomodulatory and anti-inflammatory factors in human milk. Clin Perinatol. 1999;26:361–77.
4. Gauhe A, Gyorgy P, Hoover JR, et al. Bifidus factor—preparation obtained from human milk. Arch Biochem Biophys. 1954;49:214–24.
5. Petschow BW, Talbott RD. Response of bifidobacterium species to growth promoters in human and cow milk. Pediatr Res. 1991;29:208–13.
6. Kunz C, Rudloff S, Baier W, et al. Oligosaccharides in human milk: structural, functional, and metabolic aspects. Annu Rev Nutr. 2000;20:699–722.
7. Holzapfel WH, Haberer P, Snel J, et al. Overview of gut flora and probiotics. Int J Food Microbiol. 1998;41:85–101.
8. Collins MD, Gibson GR. Probiotics, prebiotics, and synbiotics: approaches for modulating the microbial ecology of the gut. Am J Clin Nutr. 1999;69:1052S–7.
9. Gibson GR, McCartney AL. Modification of the gut flora by dietary means. Biochem Soc Trans. 1998;26:222–8.
10. Dunne C, O'Mahony L, Murphy L, et al. In vitro selection criteria for probioticbacteria of human origin: correlation with in vivo findings. Am J Clin Nutr. 2001;73:386S–92.
11. Bennet R, Nord CE, Zetterstrom R. Transient colonisation of the gut of newborn infants by orally administered bifidobacteria and lactobacilli. Acta Paediatr. 1992;81:784–7.
12. Millar MR, Bacon C, Smith SL, et al. Enteral feeding of premature infants with Lactobacillus GG. Arch Dis Child. 1993;69:483–7.
13. Langhendries JP, Detry J, Van Hees J, et al. Effect of a fermented infant formula containing viable bifidobacteria on the fecal flora composition and pH of healthy full-term infants. J Pediatr Gastroenterol Nutr. 1995;2:177–81.
14. Isolauri E, Juntunen M, Rautanen T, et al. A human Lactobacillus strain (Lactobacillus casei strain GG) promotes recovery from acute diarrhea in children. Pediatrics. 1991;88:90–7.
15. Saavedra JM, Bauman NA, Oung I, et al. Feeding of Bifidobacteriumbifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhoea and shedding of rotavirus. Lancet. 1994;44:1046–9.
16. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microflora introducing the concept of probiotics. J Nutr. 1995;125:1401–12.
17. National Institutes of Health. The NIH roadmap for medical research: the human microbiome project. http://nihroadmap.nih.gov/hmp/. Accessed 1 Nov 2010.
18. Hattori M, Taylor TD. The human intestinal microbiome: anew frontier of human biology. DNA Res. 2009;16:1–12.
19. Turnbaugh PJ, Ley RE, Hamady M, et al. The human microbiome project. Nature. 2007;449:804–10.
20. Verdu EF, Collins SM. Microbial-gut interactions in health and disease. Irritable bowel syndrome. Best Pract Res Clin Gastroenterol. 2004;18:315–21.
21. Perrier C, Corthésy B. Gut permeability and food allergies. Clin Exp Allergy. 2011;41:20–8.
22. Salminen S, Isolauri E, Salminen E. Clinical uses of probiotics or stabilizing the gut mucosal barrier: successful strains and future challenges. Antonie Van Leeuwenhoek. 1996;70:347–58.
23. Rhee KJ, Sethupathi P, Driks A, et al. Role of commensal bacteria in development of gut-associated lymphoid tissues and preimmune antibody repertoire. J Immunol. 2004;172:1118–24.
24. Suzuki K, Kawamoto S, Maruya M, et al. GALT: organization and dynamics leading to IgA synthesis. Adv Immunol. 2010;107:153–85.
25. Severson KM, Mallozzi M, Driks A, et al. B cell development in GALT: role of bacterial superantigen-like molecules. J Immunol. 2010;184:6782–9.
26. Abreu MT. Toll-like receptor signalling in the intestinal epithelium: how bacterial recognition shapes intestinal function. Nat Rev Immunol. 2010;10:131–44.
27. Collins SM, Bercik P. The relationship between intestinal microbiota and the central nervous system in normal gastrointestinal function and disease. Gastroenterology. 2009;136:2003–14.
28. Cryan JF, O'Mahony SM. The microbiome-gut-brain axis: from bowel to behavior. Neurogastroenterol Motil. 2011;23:187–92.
29. Lin HC. Small intestinal bacterial overgrowth: a framework forunderstanding irritable bowel syndrome. JAMA. 2004;292:852–8.
30. Maukonen J, Satokari R, Matto J, Soderlund H, Mattila-Sandholm T, Saarela M. Prevalence and temporal stability of selected clostridialgroups in irritable bowel syndrome in relation to predominantfaecal bacteria. J Med Microbiol. 2006;55:625–33.

31. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med. 2000;342:1500–70.
32. Mshvildadze M, Neu J, Mai V. Intestinal microbiota development in the premature neonate: establishment of a lastingcommensal relationship. Nutr Rev. 2008;66:658–63.
33. New J. Perinatal and neonatal manipulation of the intestinalmicrobiome: a note of caution. Nutr Rev. 2007;1:282–5.
34. Kirjavainen P, Gibson GR. Heathy gut microflors and allergy: factors influencing development of the microbiots. Ann Med. 1999;31:288–92.
35. Domiguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A. 2010;107:11971–5.
36. Saavedra JM. Use of probiotics in pediatrics: rationale, mechanisms of action, and practical aspects. Nutr Clin Pract. 2007;22:351–65.
37. Boeckxstaens GE. Neuroimmune interaction in the gut: from bench to bedside. Verh K Acad Geneeskd Belg. 2006;68:329–55.
38. Gewolb IH, Schwalbe RS, Taciak VL, et al. Stool microflora in extremely low birthweight infants. Arch Dis Child Fetal Neonatal Ed. 1999;80:F167–73.
39. Stark PL, Lee A. The bacterial colonization of the large bowelof pre-term low birth weight neonates. J Hygiene. 1982;89:59–67.
40. Buchen L. The new germ theory. Nature. 2010;468:492–5.
41. Wang Y, Hoenig JD, Malin KJ, et al. 16S rRNA gene-basedanalysis of fecal microbiota from preterm infants with andwithout necrotizing enterocolitis. ISME J. 2009;3:944–54.
42. Morowitz MJ, Poroyko V, Caplan M, et al. Redefining the role of intestinal microbes in the pathogenesisof necrotizing enterocolitis. Pediatrics. 2010;125:777–85.
43. Berseth CL. Gastrointestinal motility in the neonate. Clin Perinatol. 1996;23:179–90.
44. Lucas A, Cole TJ, Morley R, et al. Factors associated with maternal choice to provide breast milk for low birthweight infants. Arch Dis Child. 1988;63:48–52.
45. Dumont RC, Rudolph CD. Development of gastrointestinal motility in the infant and child. Gastroenterol Clin North Am. 1994;23:655–71.
46. Piena-Spoel M, Albers MJ, Ten Kate J, Tibboel D. Intestinal permeability in newborns with necrotizing enterocolitis and controls: does the sugar absorption test provide guidelines to (re-)introduce enteral nutrition? J Pediatr Surg. 2001;36:587–92.
47. Neu J. Gastrointestinal development and meeting the nutritional needs of premature infants. Am J Clin Nutr. 2007;85(suppl):629S–34.
48. Lebenthal A, Lebenthal E. The ontogeny of the small intestinal epithelium. JPEN J Parenter Enteral Nutr. 1999;23:S3–6.
49. Berseth CL, Nordyke CK, Valdes MG, et al. Responses of gastrointestinal peptides and motor activity to milk and water feedings in preterm and term infants. Pediatr Res. 1992;31:587–90.
50. Newburg DS. Neonatal protection by innate immune system of human milk consisting of oligosaccharides and glycans. J Anim Sci. 2009;87:26–34.
51. Martin R, Langa S, Reviriego C, et al. Human milk is a source of lactic acid bacteria for the infant gut. J Pediatr. 2003;143:754–8.
52. Bruzzese E, Volpicelli M, Salvini F, et al. Early administration of GOS/FOS prevent intestinal and respiratory infections in infants. J Pediatr Gastroenterol Nutr. 2006;42:2–18.
53. Forchielli ML, Walker WA. The role of gut-associated lymphoid tissues and mucosal defence. Br J Nutr. 2005;93 Suppl 1:S41–8.
54. Labayen I, Forga L, Gonzalez A, et al. Relationship between lactose digestion, gastrointestinal transit time and symptoms in lactose 30 malabsorbers after dairy consumption. Aliment Pharmacol Ther. 2001;15:543–9.
55. Clark DA, Miller MJ. Intraluminal pathogenesis of necrotizing enterocolitis. J Pediatr. 1990;117:64–7.
56. Savilahti E, Kuitunen M, Vaarala O. Pre and probiotics in the prevention and treatment of food allergy. Curr Opin Allergy Clin Immunol. 2008;8:243–8.
57. Furrie E, Macfarlane S, Kennedy A, et al. Symbiotic therapy (bifidobacteriumlongum/Sinergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: a randomized controlled pilot trial. Gut. 2005; 54:242–9.
58. Lu L, Walker WA. Pathogenic and physiologic interactions of bacteria with the gastrointestinal epithelium. Am J Clin Nutr. 2001;73:1124S–30.
59. Sherman MP. New concepts of microbial translocation in the neonatal intestine: mechanisms and prevention. Clin Perinatol. 2010;37:565–79.
60. Madsen K, Cornish A, Soper P, et al. Probiotic bacteria enhance murine and human intestinal epithelial barrier function. Gastroenterology. 2001;121:580–91.

61. Wehkamp J, Harder J, Wehkamp K, et al. Nf-kB and AP-1-mediated induction of human beta defensin-2 in intestinal epithelial cells by Escherichia coli Nissle 1917: a novel effect of a probiotic bacterium. Infect Immun. 2004;72:5750–8.
62. Arslanoglu S, Moro GE, Schmitt J, et al. Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. J Nutr. 2008;138:1091–5.
63. Sherman PM, Cabana M, Gibson GR, et al. Potential roles and clinical utility of prebiotics in newborns, infants, and children: proceedings from a global prebiotic summit meeting, New York City, June 27–28, 2008. J Pediatr. 2009;155:S61–70.
64. Schauber J, Svanholm C, Termen S, et al. Expression of the cathelicidin LL-37 is modulated by short chain fatty acids in colonocytes: relevance of signalling pathways. Gut. 2003;52:735–41.
65. Raqib R, Sarker P, Bergman P, et al. Improved outcome in shigellosis asociated with butyrate induction of an endogenous peptide antibiotic. Proc Natl Acad Sci U S A. 2006;103:9178–83.
66. Weizman Z, Alsheikh A. Safety and tolerance of a prebiotic formula in early infancy comparing two probiotic agents: a pilot study. J Am Coll Nutr. 2006;25:415–9.
67. Schwartz GJ, Moran TH. Duodenal nutrient exposure elicits nutrient-specific gut motility and vagal afferent signals in rats. Am J Physiol. 1998;274:R1236–42.
68. Bouin M, Savoye G, Maillot C, et al. How do fiber-supplemented formulas affect antroduodenal motility during enteral nutrition? A comparative study between mixed and insoluble fibers. Am J Clin Nutr. 2000;72:1040–6.
69. McManus CM, Michel KE, Simon DM, et al. Effect of short chain fatty acids on contraction of smooth muscle in the canine colon. Am J Vet Res. 2002;63:295–300.
70. Cherbut C. Motor effects of short-chain fatty acids and lactate in the gastrointestinal tract. Proc Nutr Soc. 2003;62:95–9.
71. Longo WE, Ballantyne GH, Savoca PE, et al. Short-chain fatty acid release of peptide YY in the isolated rabbit distal colon. Scand J Gastroenterol. 1991;26:442–8.
72. Ravelli AM, Tobanelli P, Volpi S, et al. Vomiting and gastric motility in infants with cow's milk allergy. J Pediatr Gastroenterol Nutr. 2001;32:59–64.
73. Clark DA, Miller MJ. Intraluminal pathogenesis of necrotizing enterocolitis. J Pediatr. 1990;117:s64–7.
74. Guerrini S, Barbara G, Stanghellini V, et al. Inflamatory neuropathies of the enteric nervous system. Gastroenterology. 2004;126:1872–83.
75. Wang XY, Berezin I, Mikkelsen HB, et al. Pathology of interstitial cells of Cajal in relation to inflammation reveald by ultrastructure but not immunochemistry. Am J Pathol. 2002;160:1529–40.
76. Verdue E, Bergonzelli G, Bercik P, Lopes L, Fürholz A, Rochat F, Corthésy-theulaz I, Collins S. Lactobacillus paracaseii normalizes postinfectivedismotility in vivo- Potential mechanism involved. J Pediatr Gastroenterol Nutr. 2006;42:E96.

Part III
Hormones and Lipids: Growth and Development of Infants

Chapter 23
General Area of Lipid Composition of Diets to Optimize Growth and Development of Premature Infants

Girish Deshpande and Rajesh Maheshwari

Key Points for Parenteral Lipid Emulsions (LE)

- Significant research has been performed in understanding the composition, dose, and clinical effects of parenteral lipid in neonatal patients, since the first LEs were introduced in the 1960s.
- Newer LE may have short-term clinical benefits in reducing lipid peroxidation and inflammation, and FO-based LEs have shown benefits in the treatment of parenteral nutrition-induced neonatal cholestasis.
- Considering that there is lack of data in terms of definitive head to head trials of different novel LEs evaluating short- as well as long-term clinically important outcomes including neurodevelopment, further research in this area is urgently needed.
- At this stage it is unclear if there are any long-term benefits of introducing costly newer LEs in preterm neonates as compared to standard SO-based LEs.

Key Points for Enteral Lipid Composition in Diet of Preterm Neonates

- The current research in the diet of preterm neonates is based to define and provide optimum LC-PUFA intake, primarily that of DHA and AA.
- Although small individual studies showed benefits in short-term growth, vision, and developmental outcomes, data from Cochrane and IPD meta-analysis suggest otherwise.
- In the absence of clear evidence, an LC-PUFA recommendation in preterm neonates is still a controversial area and is constantly evolving.
- Adequately powered large RCTs combining parenteral and enteral interventions are required to evaluate the long-term benefits of LC-PUFA supplementation in preterm neonates.

Keywords Premature infants • Lipid composition • PUFAs • Human milk • DHA

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Abbreviations

LEs	Lipid emulsions
OO	Olive oil
FO	Fish oil
SO	Soybean oil
EFA	Essential fatty acids
PUFA	Polyunsaturated fatty acids
LA	Linoleic acid
ALA	Alpha linolenic acid
LC-PUFAs	Long chain polyunsaturated fatty acids
MCT	Medium chain triglycerides
DHA	Docosahexaenoic acid
AA	Arachidonic acid
EPA	Eicosapentaenoic acid

Introduction

Preterm neonates particularly extremely low birth weight (ELBW: <1,000 g birth weight) group is the major cause of perinatal mortality and morbidity [1]. Major innovations in neonatology during the past three decades have improved the survival of high-risk neonates significantly. Feeding intolerance is a common issue in preterm neonates, and in those with conditions such as necrotizing enterocolitis (NEC), gastroschisis, and short bowel syndrome. Long-term support with parenteral nutrition (PN) is crucial for this population of neonates to provide optimal nutrition at a critical stage of development [2].

In the last two decades, there has been considerable interest in the role of lipids in infant development. Fatty acids play central roles in growth and development through their roles in membrane lipids, as ligands for receptors and transcription factors that regulate gene expression, precursor for eicosanoids, in cellular communication, and through direct interactions with proteins [3]. The preterm neonate is born during critical period of brain growth. Processes such as cellular migration, myelination, and cellular differentiation may all be susceptible to nutritional deprivation during this period. Intravenous lipid emulsions (LEs) may be the only source of essential fatty acids (EFAs), linoleic acid (LA), and alpha linolenic acid (ALA) for parenterally fed preterm neonates. LEs have been in use for almost 50 years [4]. LEs provide a concentrated source of energy. For preterm and term neonates, LEs at a dose of 2–3 g/kg/day could satisfy 20–30% of daily caloric requirement. Some LEs also contain long chain polyunsaturated fatty acids (LC-PUFAs), whose endogenous synthesis may be limited in the neonatal period [5, 6]. Lipid emulsions also influence immune cell functions at various levels including cell membrane properties, phagocytosis, and production of bioactive substances such as cytokines [7].

In recent years, there have been many advances in the area of parenteral lipid emulsions used in total parenteral nutrition for preterm infants. While long-term data are lacking, some short-term benefits have been noted. This chapter aims to focus on the lipid composition of the diet of the preterm neonates (both enteral and parenteral) and its potential effect on growth and neurodevelopment of these vulnerable infants.

Composition of Lipid Emulsions Commonly Used in Preterm Neonates

The earliest LEs for neonates were soybean oil (SO) based and were developed in the early 1960s. For the purpose of this chapter SO-based LEs will be referred as "standard LEs," as they are still used widely. SO-based LEs contain predominantly n-6 fatty acids (52–55%). Excess n-6 fatty acids and their metabolites result in pro-inflammatory eicosanoid production and have the potential to increase lipid peroxidation [8, 9]. Preterm neonates are more vulnerable to oxidative injury due to limited anti-oxidative capacity and exposure to other risk factors during their stay in the intensive care [9, 10].

Subsequent development of LEs was focused on reducing the amount of SO (n-6 fatty acids) and replacing SO with other oils including coconut oil (rich in medium chain triglyceride-MCT), olive oil (OO-rich in n-9 fatty acid), and fish oil (FO-rich in n-3 fatty acids) (Table 23.1). Several fish oil (FO) based LEs are available including those containing exclusively FO (Omegaven), combination of FO, OO, MCT, and SO oils (SMOFlipid), and combination of FO, MCT, and SO (Lipoplus).

Role of Olive Oil-Based LEs in Preterm Neonates on Short-Term Outcomes, Growth, and Development

Various health benefits in Mediterranean diet rich in olive oil are well known in adult population [11]. OO-based LE (Clinoleic® Baxter Pharmaceuticals) contains OO (OO: SO ratio of 4:1) with a PUFA content only a third of that in the standard SO emulsion. OO-based LEs contain predominantly mono-unsaturated fatty acids (MUFA) which are potentially more resistant to free radical attack and have additional anti-inflammatory properties which could be beneficial in preterm neonates, who are usually exposed to stressful environment in the neonatal intensive care [12]. OO-based LEs are also rich in vitamin E content which has anti-oxidant properties which could be of added benefit in attenuating potential oxidation injury in preterm neonates [13, 14]. SO-based LEs are rich in omega-6 fatty acids which are the precursors of proinflammatory prostaglandin E2 and leukotriene B4 and also influence cytokine synthesis [15].

It has been postulated that the use of OO lipid emulsion could be as efficient as standard SO lipid emulsion in supplying EFA and LC-PUFAs including docosahexaenoic acid (DHA) and arachidonic acid (AA). This was first confirmed by an RCT comparing OO-based LEs to standard SO-based LEs in preterm neonates more than 28 weeks ($n=33$, SO:15 and OO:18) [16]. However there was no significant difference in oxidative stress levels measured by urinary MDA levels. Deshpande et al. have reported an RCT comparing OO-based LEs with SO-based LEs in very preterm infants (Gestation: <28 weeks) [17]. Primary outcome of this trial was comparison of plasma and RBC fatty acids levels and oxidative stress levels (F_2-isoprostanes) between the two groups. Forty-four of fifty participants (OO-23, SO-21) completed the trial. Both LEs were well tolerated without any adverse events. F_2-isoprostane levels were comparable in both groups. Oleic acid and LA levels were significantly higher in OO and SO groups, respectively. LC-PUFA levels were similar between groups despite the lower PUFA content of OO. OO group had significantly higher levels of RBC and plasma fatty acid C18:4n-3, suggesting possible Δ6-desaturase enzyme inhibition in SO group.

Roggero et al. conducted a three arm RCT in preterm neonates (Gestation: 28–33 weeks) randomized to receive either SO-based LEs, or OO-based LE (Clinoleic®), or SO/MCT-based LE [18]. The oxidative stress levels measured by the F_2-isoprostanes and total radical-trapping antioxidant (TRAP) concentration were not significantly different in the three groups.

The safety of OO LEs in critically ill preterm and term neonates has been documented by these RCTs [16–18]. In theory, OO emulsions have the potential to reduce the oxidative stress while enhancing the anti-inflammatory effects (due to its high MUFA content). The short-term outcome

Table 23.1 Oil combinations used to formulate the currently available lipid emulsions (percentage of lipid)

	Intralipid	Lipofundin	Lipoplus	SMOFLipid	Clinoleic	Omegaven
Soy oil	100	50	40	30	20	0
Olive oil	0	0	0	25	80	0
Medium chain triglycerides	0	50	50	30	0	0
Fish oil	0	0	10	15	0	100

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results from RCTs in preterm neonates did not show any significant difference in oxidative stress compared to standard SO emulsion.

Another RCT in preterm neonates (<32 weeks, <1,500 g) by Gawecka et al. compared inflammatory effects, including tumor necrosis factor-alpha (TNF-α) and interleukins (IL-6, IL-10), between SO- and OO-based LEs [19]. Baseline cytokine levels were comparable in the two groups; however, pro-inflammatory cytokine levels (IL-6) were significantly higher in the SO group. Other secondary outcomes including the incidence of bronchopulmonary dysplasia, necrotizing enterocolitis, and retinopathy of prematurity (ROP) were similar in both groups.

All studies report comparing OO-based LEs with standard SO-based LEs compared only short-term biochemical outcomes and early growth parameters. Data on long-term growth and developmental outcomes including vision is lacking in all studies.

Role of Fish Oil-Based LEs in Preterm Neonates on Short-Term Outcomes, Growth, and Development

Recently there has been considerable interest in FO-based LEs which are rich in omega-3 fatty acids known for anti-inflammatory properties [20]. Currently FO-based LEs are available in various preparations (Table 23.1). Standard SO-based LEs are rich in PUFAs especially LA with the potential to increase lipid peroxidation [8, 21]. Preterm neonates are more vulnerable to oxidative injury due to limited anti-oxidative capacity and exposure to other risk factors during their stay in the intensive care [22, 23]. Newer FO-based LEs such as SMOFLipid® (Table 23.1 for composition) have potential to reduce lipid peroxidation due to the presence of MCTs, and an appropriate amount of antioxidant alpha-tocopherol and MUFAs [22]. FO-based LEs are a rich source of n-3 LC-PUFAs including DHA and eicospentaenoic acid (EPA) with associated anti-inflammatory properties [24]. The eicosanoids produced from n-3 LC-PUFAs are less inflammatory compared to those originating from n-6 LCPUFAs [25].

Early experience in pediatric patients with intestinal failure associated liver disease suggests that FO-based LEs are useful in the prevention and treatment of cholestasis associated with PN [26]. This issue is not discussed further in this chapter as it will be covered in Chapter 25.

Tomsits et al. recently reported an RCT documenting safety of FO-based LEs in preterm neonates ($n = 60$, age 3–7 days, gestation <≠34 weeks, birth weight 1,000–2,500 g) comparing FO-based LE (SMOFLipid®) with standard SO-based LE [27]. There was no difference in adverse events, serum triglycerides, or local tolerance (when infused peripherally) confirming the safety of study treatment. Gamma-glutamyl transferase (GGT) was lower, and omega-3 fatty acids in red blood cell phospholipids were higher in the study versus the control group. Plasma alpha-tocopherol was also raised in the study group, suggestive of possible anti-inflammatory effects of FO-based LEs.

In a study by Skouroliakou et al., 38 preterm neonates (Gestation <32 weeks, birth weight <1500 g) were randomized to receive SMOFLipid emulsion or pure SO-based LE (Intralipid) for at least 7 days [28]. Significant reduction in oxidative stress in the SMOFlipid group was documented by a significant rise in alpha-tocopherol and total anti-oxidant potential levels compared with standard LE. A recent

observational study has shown that fish-oil-based fat emulsion administered from the first day of life may be effective in the prophylaxis of severe ROP requiring laser therapy. Prospective data about severity and treatment of ROP from 40 preterm neonates (<1,250 g) who received FO-based LEs were compared with similar historical data from 44 preterm neonates who received SO- and OO-based LEs. There was a significantly lower risk of laser therapy for infants who received an emulsion of fish oil. No significant differences were found in acuity and latency of visual evoked potentials between the infants in the two groups.

Although none of the neonatal studies have documented specific immunological effects of FO-based LEs, several adult and animal studies have reported benefits in terms of anti-inflammatory effects in critically ill/septic patients [30, 31].

At this stage long-term growth and development data are lacking from the current trials with FO-based LEs; however, there are encouraging short-term benefits including low oxidative stress levels and possible benefits in reducing severity of ROP.

Intravenous Lipid Dose in Early Life

In order to prevent EFA deficiency, preterm neonates need at least 0.25 g/kg/day of intravenous (IV) LEs in the first week of life. Currently there is no clear consensus for initial lipid dose and increments in the first week of life. An RCT by Drenckpohl et al. compared high- vs. low-dose IV lipids in 110 preterm neonates (birth weight 750–1,500 g) [31]. Neonates in the high-dose group received 2 g/kg/day of IV LEs as a starting dose when compared with 0.5 g/kg/day in the control group IV LEs were increased by 0.5 g/kg/day up to 3 g/kg/day in both groups. The high-dose group had significantly higher energy intake without a significant difference in serum triglyceride (TG) levels (>200 mg/dL) compared to the control group. Considering the importance of postnatal malnutrition and growth retardation within first week of life [32], starting lipid in the first few days of life at 2 g/kg/day appears safe, and, although it seems it could be beneficial, recent Cochrane review suggests otherwise [33].

Summary and Future Research

Newer LEs may have short-term clinical benefits in terms of reducing lipid peroxidation and inflammation. In addition to these benefits, newer FO-based LEs have shown benefits in the treatment of intestinal failure associated liver disease. However, at this stage it is unclear if there are any long-term benefits of introducing costly newer LEs in preterm neonates and other high risk populations such as neonates with surgical conditions.

Considering there is lack of data in terms of definitive head to head trials of different novel LEs evaluating short- as well as long-term clinically important outcomes including neurodevelopment, further research in this area is urgently needed.

Lipid Composition for Preterm Enteral Nutrition

Modification of the lipid content of the diet in preterm infants in an attempt to improve growth, vision, and neurodevelopment has been tried for more than 20 years. The major thrust of the research has been to define and provide optimum LC-PUFA intake, primarily that of DHA and AA [3]. DHA is enriched in brain gray matter and retina phospholipids, and it represents 3–5% of the dry weight of these tissues [34]. Dietary deficiency of n-3 fatty acids decreases brain and retina DHA, impairs

neurogenesis, alters gene expression and neurotransmitter, including dopamine and serotonin metabolism, and decreases the kinetics of the visual photocycle [35]. Their accretion occurs primarily during the last trimester of pregnancy and the first year of life [36]. While a breastfed full-term neonate receives its full allowance of LC-PUFA, first through placenta and then via breast milk, a preterm neonate is at a disadvantage in not receiving optimum LC-PUFA at a time when the brain is growing rapidly. Formula fed infants have significantly lower DHA levels in their red blood cells and cerebral cortex compared with breast fed infants [37]. This is despite the presence of EFAs LA and ALA in the formula which are the precursors of AA and DHA, respectively. This is attributed to the relative inefficiency of LC-PUFA synthesis from its precursors in neonates. Not surprisingly, the studies have focused on the preterm infant and formula fed term infant. For the purpose of this chapter, we focus on the studies in preterm infants, both breast and formula fed.

LC-PUFA Supplementation in Formula Fed Preterm Infants and Their Effect on Vision and Neurodevelopment

Evidence from biochemical studies in both term and preterm neonate indicates that formula fed infants have significantly less DHA and AA in their erythrocytes relative to those fed breast milk [38]. In a prospective observational study, term neonates fed breast milk have been found to have more mature visual acuities and higher DHA levels than those receiving formula. Further, their acuities were positively correlated with erythrocyte DHA levels [39].

Multiple studies in the last two decades have looked at infant and toddler development after LC-PUFA supplementation in the formula for preterm neonates. The methods of assessment have included Fagan Test of Infant Intelligence and Bayley Scale of Infant and Toddler Development (BSID). In an RCT in preterm infants fed DHA until 9 months, novelty preference was not affected but the supplemented group demonstrated shorter look duration suggesting faster information processing [40]. Thus, it was theorized that information processing, rather than memory or learning ability may be affected by DHA supplements. Woltil et al. investigated the effect of 2 different doses of LC-PUFA (0.43% DHA and 0.34% EPA) given from birth to 6 weeks of age on the development of low birth weight infants and found improved BSID scores at 19 months of age in the group fed with higher PUFA dose [41]. In an RCT by Fewtrell et al. in preterm neonates with birth weights <1,750 g, study group received preterm formula supplemented with vegetable oils and milk fat with derivatives of LA and ALA sourced from evening primrose oil and egg lipids. Control group received unsupplemented preterm formula. Breast milk fed preterm infants served as a reference group. Main outcome measures were Bailey MDI and PDI at 18 months and Knobloch, Passamanick, and Sherrard's Developmental Screening Inventory at 9 months corrected age [42]. No statistically significant differences were noted. The same group conducted another trial utilizing tuna oil (as DHA source) and borage oil (as a source for ALA, which is a precursor of AA) in the supplemented group. Primary efficacy outcome was neurodevelopment at 18 months corrected age as assessed by Bayley PDI and MDI scores. No significant difference was found [43]. Clandinin et al. used two different sources of DHA (algal oil, fish oil) but same source of AA (fungal oil) in their trial. Control group was not supplemented and breast fed term infants served as a reference group. Supplemented groups had higher Bayley MDI and PDI scores at 118 weeks post-menstrual age as compared to the control group [44].

Recently a Cochrane review was conducted by Schulzke et al., and they found 17 eligible RCTs in preterm neonates <37 weeks receiving LC-PUFA supplemented formula [45]. However, the included trials varied in their assessment schedule and methodology, dose and source of LC-PUFA used and the fatty acid composition of the control formula. The clinical outcomes assessed in the studies of LC-PUFA supplementation have included growth, visual function, and neurodevelopment. Three out

of seven studies reported some benefit of LCPUFA on neurodevelopment in different populations at different postnatal ages. Meta-analysis of Bayley Scales of Infant Development of four studies at 12 months ($N=364$) and three studies at 18 months ($N=494$) post-term showed no significant effect of supplementation on neurodevelopment. One of the limitations of this meta-analysis was the broad selection criteria (preterm neonates <37 weeks). The trials included in the meta-analysis had enrolled preterm infants that were relatively mature and healthy. As infants with the lowest birth weight are at the highest risk for severe DHA deficiency, any treatment effect is likely to be masked if the study population comprises relatively mature infants. Also, the trials have varied in assessment schedule and methodology, dose and source of fatty acid supplementation, and composition of the control formula. Hence reliability of the conclusions of meta-analyses of LC-PUFA supplementation is debatable.

In order to specifically look for effect of LC-PUFA supplementation in preterm VLBW neonates, an individual patient data (IPD) meta-analysis was conducted by Beyerlein et al. [46]. An IPD meta-analysis was performed on 870 infants from four trials; subgroup analyses by preterm delivery and very low birth weight (<1,500 g) were also conducted ($n=371$). There were no significant differences in Bayley MDI and PDI scores between LCPUFA-supplemented and control groups for all children or in subgroups (preterm VLBW neonates). This was confirmed with adjustment for the possible confounders: sex, gestational age, birth weight, maternal age, and maternal smoking.

Effects of LC-PUFA Supplementation on Growth of Preterm Neonates

There are various possible mechanisms whereby dietary PUFA and LC-PUFA can affect growth. These involve prostaglandins, growth hormone, and biosynthesis of membrane components [47]. AA is a major constituent of membrane lipids and an eicosanoid precursor. Variations in AA and eicosanoid levels may have effect on muscle protein turnover. LC-PUFA may also have a role in gene expression for adipocyte development. Assessment of growth has been a safety as well as an efficacy measure in the trials of LC-PUFA supplementation in preterm infants. Initial concerns were raised about the negative impact of a marine oil supplemented formula on the growth of infants [48]. The oil contained DHA and EPA but no AA. A subsequent publication from these authors noted declining levels of AA in growing preterm infants on commercial formula and the decline to be more pronounced in the marine oil supplemented group [40]. This led them to conclude that a conditional deficiency of AA may have contributed to poor growth in preterm infants. Most of the subsequent trials have used a combination of DHA and AA in the supplemented group and the negative effect on growth has not largely been seen. Recent Cochrane review included five studies with LC-PUFA supplementation in preterm neonates [45]. Four out of five studies reported benefits of LCPUFA on the growth of supplemented infants at different postnatal ages. Two trials suggested that LCPUFA supplemented infants grow less well than controls. One trial reported mild reductions in length and weight z scores at 18 months. Meta-analysis of five studies showed increased weight and length at 2 months post-term in supplemented infants. However, when they compared growth outcomes at 12 months ($N=271$, four studies) and 18 months ($N=396$, two studies) post-term, it showed no significant effect of supplementation on weight, length, or head circumference. Authors concluded that on pooling of results, no clear long-term benefits or harms were demonstrated for preterm infants receiving LCPUFA-supplemented formula. IPD meta-analysis of 4 RCTs of LC-PUFA supplementation on infant growth ($n=901$) showed no evidence that LC-PUFA supplementation affects children's growth at 18 months of age after adjustment for possible confounders including sex, gestational age, birth weight, smoking in the last trimester, and maternal age [49].

LC-PUFA Supplementation in Breast Milk Fed Preterm Infants

The majority of studies for supplementing LC-PUFA for preterm infants have focused on formula fed preterm infants as human milk has preformed LC-PUFA. However, two recent studies have looked at increasing LC-PUFA intake of human milk fed preterm infants also. The rationale includes variable content of DHA in human milk and reduced bioavailability of DHA from enteral route as opposed to placental bioavailability. Henriksen et al. fortified human milk with DHA and AA in a randomized study in VLBW infants [50]. At the 6-month follow-up evaluation, the study group performed better than the control group in the problem-solving subscore of the Ages and Stages Questionnaire. In another multi-center RCT preterm infants (<33 weeks) were randomized to high versus standard DHA group (1 vs. 0.35% of fatty acids) [51]. Lactating mothers took capsules containing 3 g of either DHA-rich tuna oil (900 mg of DHA) or soy oil (no DHA). If supplemental formula was required, infants in the intervention group were given a high DHA preterm formula (~1% DHA and 0.6% AA). Of the 657 infants included in the trial, 93.5% were assessed at 18 months corrected age by BSID. No overall differences in Bayley MDI and PDI scores were observed between groups, but there was a trend toward improved MDI scores in the infants with birth weight <1,250 g in the high DHA group.

Safety Considerations for Enteral LC-PUFA Supplementation

As discussed in the previous section, reduced weight and linear growth were noted in an earlier study of LCP supplementation [48]. However, with the exception of one study, no adverse impact on growth has been seen when both DHA and AA have been supplemented [42]. No specific adverse events were noted in the intervention and control groups in a recent systematic review [45]. Similarly, no increase in NEC, IVH, ROP, or sepsis was noted when investigating the effects of a higher dose of DHA [51]. Overall, it appears that DHA and AA supplements as used in the current studies in preterm infants are safe.

LC-PUFA Recommendations in Preterm Formulas

In the absence of a clear evidence, an LC-PUFA recommendation in preterm neonates is still a controversial area and is constantly evolving. The reference standard is the content of these fatty acids in the breast milk. While the content of AA in breast milk is fairly constant at about 0.45% of total fatty acids, the content of DHA is variable (0.1–3.8%) based on the maternal diet [52]. The dose of DHA used in various trials included in Cochrane review has ranged from 0.05 to 0.76% of fatty acids [45].

In a recent elegant review, the authors estimated that fetal DHA accretion rate during the last trimester of pregnancy is close to 45 mg/kg/day [53]. They also mention that enterally fed premature infants exhibit daily DHA deficit of 20 mg/kg/day, representing 44% of the DHA that should have been accumulated. Therefore, the DHA content of human milk and current preterm formulas cannot compensate for an early DHA deficit which may occur during the first month of life and is also unable to fulfill the DHA requirement of growing preterm infants. Based on the results of the two dose–response studies, they recommend increasing the DHA content of human milk to a value of 1.1% total fatty acids, since this should fulfill the DHA requirement and appears to be safe [50, 51].

Summary and Future Research

It appears that DHA and AA supplements as used in the current studies in preterm infants are safe; however, the present data are insufficient to recommend a specific amount of LC-PUFAs in preterm neonates. Further research is also needed to determine the amount of arachidonic acid which should be consequently given to enterally and parenterally fed preterm infants to avoid a conditional deficiency of AA. Adequately powered large RCTs are required to evaluate long-term benefits of LC-PUFA supplementation in preterm neonates. This may include combining two interventions, LC-PUFA-rich intravenous LEs and LC-PUFA supplementation in breast milk and formula in preterm neonates.

References

1. Hintz SR, Kendrick DE, Stoll BJ, Vohr BR, Fanaroff AA, Donovan EF, Poole WK, Blakely ML, Wright L, Higgins R, NICHD Neonatal Research Network. Neurodevelopmental and growth outcomes of extremely low birth weight infants after necrotizing enterocolitis. Pediatrics. 2005;115:696–703.
2. Wessel JJ, Kocoshis SA. Nutritional management of infants with short bowel syndrome. Semin Perinatol. 2007;31(2):104–11.
3. Innis SM. Fatty acids and early human development. Early Hum Dev. 2007;83:761–6.
4. Driscoll DF. Lipid injectible emulsions. Nutr Clin Pract. 2006;21:381–6.
5. Uauy R, Hoffman DR, Peirano P, et al. Essential fatty acids in visual and brain development. Lipids. 2001;36:885–95.
6. McNamara RK, Carlson SE. Role of omega-3 fatty acids in brain development and function and function: potential implication for pathogenesis and prevention of psychopathology. Prostaglandins Leukot Essent Fatty Acids. 2006;75:329–49.
7. Yaqoob P. Fatty acids and the immune system: from basic science to clinical applications. Proc Nutr Soc. 2004;63:89–104.
8. Eritsland J. Safety considerations of polyunsaturated fatty acids. Am J Clin Nutr. 2000;71(1 Suppl):197S–201.
9. Sweeney B, Puri P, Reen DJ. Modulation of immune cell function by polyunsaturated fatty acids. Pediatr Surg Int. 2005;21:335–40.
10. Heird WC. Biological effects and safety issues related to long chain polyunsaturated fatty acids in infants. Lipids. 1999;34(2):207–14.
11. Pérez-Martínez P, García-Ríos A, Delgado-Lista J, Pérez-Jiménez F, López-Miranda J. Mediterranean diet rich in olive oil and obesity, metabolic syndrome and diabetes mellitus. Curr Pharm Des. 2011;17(8):769–77.
12. Deshpande G, Simmer K. Lipids for parenteral nutrition in neonates. Curr Opin Clin Nutr Metab Care. 2011;14(2):145–50.
13. Sala-Vila A, Barbosa VM, Calder PC. Olive oil in parenteral nutrition. Curr Opin Clin Nutr Metab Care. 2007;10:165–74.
14. Goulet O, de Potter S, Antébi H, et al. Long-term efficacy and safety of a new olive oil-based intravenous fat emulsion in pediatric patients: a double-blind randomized study. Am J Clin Nutr. 1999;70:338–45.
15. Kinsella JE, Broughton S, Whelan JW, et al. Dietary fatty acids: interaction and possible needs in relation to eicosanoid synthesis. J Nutr Biochem. 1995;1:123–41.
16. Göbel Y, Koletzko B, Böhles HJ, et al. Parenteral fat emulsions based on olive and soybean oils: a randomized clinical trial in preterm infants. J Pediatr Gastroenterol Nutr. 2003;37(2):161–7.
17. Deshpande GC, Simmer K, Mori T, Croft K. Parenteral lipid emulsions based on olive oil compared with soybean oil in preterm (<28 weeks' gestation) neonates: a randomised controlled trial. J Pediatr Gastroenterol Nutr. 2009;49:619–25.
18. Roggero P, Mosca F, Giannì ML, et al. F2-isoprostanes and total radical-trapping antioxidant potential in preterm infants receiving parenteral lipid emulsions. Nutrition. 2010;26:551–5.
19. Gawecka A, Michalkiewicz J, Kornacka MK, et al. Immunologic properties differ in preterm infants fed olive oil vs. soy-based lipid emulsions during parenteral nutrition. J Parenter Enteral Nutr. 2008;32:448–53.
20. Grimm H, Mertes N, Goeters C, et al. Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients. Eur J Nutr. 2006;45:55–60.
21. Halliwell B. Oxidative stress, nutrition and health. Experimental strategies for optimization of nutritional antioxidant intake in humans. Free Radic Res. 1996;25:57–74.

22. Varsila E, Hallman M, Andersson S. Free-radical-induced lipid peroxidation during the early neonatal period. Acta Paediatr. 1994;83:692–5.
23. Saugstad OD. Oxidative stress in the newborn-a 30 year prospective. Biol Neonate. 2005;88:228–36.
24. Mirtallo JM, Dasta JF, Kleinschmidt KC, Varon J. State of the art review: intravenous fat emulsions: current applications, safety profile, and clinical implications. Ann Pharmacother. 2010;44:688–700.
25. Wanten GJ, Calder PC. Immune modulation by parenteral lipid emulsions. Am J Clin Nutr. 2007;85:1171–84. http://www.unscn.org/files/Working_Groups/Micronutrients/Other_material/INACG_efficacy_and_effectiveness.pdf. Accessed 11 october 2012.
26. Gura KM, Lee S, Valim C, et al. Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. Pediatrics. 2008;121:678–86.
27. Tomsits E, Pataki M, Tölgyesi A, et al. Safety and efficacy of a lipid emulsion containing a mixture of soybean oil, medium-chain triglycerides, olive oil, and fish oil: a randomised, double-blind clinical trial in premature infants requiring parenteral nutrition. J Pediatr Gastroenterol Nutr. 2010;51(4):514–21.
28. Skouroliakou M, Konstantinou D, Koutri K, et al. A double-blind, randomized clinical trial of the effect of omega-3 fatty acids on the oxidative stress of preterm neonates fed through parenteral nutrition. Eur J Clin Nutr. 2010;64:940–7.
29. Pawlik D, Lauterbach R, Turyk E. Fish-oil fat emulsion supplementation may reduce the risk of severe retinopathy in VLBW infants. Pediatrics. 2011;127(2):223–8.
30. De Nardi L, Bellinati-Pires R, Torrinhas RS, et al. Effect of fish oil containing parenteral lipid emulsions on neutrophil chemotaxis and resident-macrophages' phagocytosis in rats. Clin Nutr. 2008;27:283–8.
31. Antébi H, Mansoor O, Ferrier C, et al. Liver function and plasma antioxidant status in intensive care unit patients requiring total parenteral nutrition: comparison of 2 fat emulsions. J Parenter Enteral Nutr. 2004;28:142–8.
32. Embleton N, Pang N, Cooke R. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatrics. 2001;107(2):270–3.
33. Simmer K, Rao SC. Early introduction of lipids to parenterally fed preterms infants. Cochrane Rev. 2005: CD005256
34. Innis SM. Essential fatty acid metabolism during early development. In: Burrin DG, editor. Biology of metabolism in growing animals. Amsterdam: Elsevier Science B.V; 2005. p. 235–74. Part III.
35. Innis SM. Dietary n-3 fatty acids and brain development. J Nutr. 2007;137:855–9.
36. Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW. Intrauterine fatty acid accretion rates in human brain: implications for fatty acid requirements. Early Hum Dev. 1980;4(2):121–9.
37. Makrides M, Neumann MA, Byard RW, Simmer K, Gibson RA. Fatty acid composition of brain, retina, and erythrocytes in breast- and formula-fed infants. Am J Clin Nutr. 1994;60:189–94.
38. Clark KJ, Makrides M, Neumann MA, Gibson RA. Determination of the optimal ratio of linoleic acid to alpha linolenic acid in infant formulas. J Pediatr. 1992;120:S151–8.
39. Makrides M, Simmer K, Goggin M, Gibson RA. Erythrocyte docosahexaenoic acid correlates with the visual response of the healthy, term infant. Pediatr Res. 1993;33:3242–53.
40. Carlson SE, Werkman SH. A randomized trial of visual attention of preterm infants fed docosahexaenoic acid until two months. Lipids. 1996;31(1):85–90.
41. Woltil HA, van Beusekom CM, Okken-Beukens M, et al. Development of low-birthweight infants at 19 months of age correlates with early intake and status of long-chain polyunsaturated fatty acids. Prostaglandins Leukot Essent Fatty Acids. 1999;61(4):235–41.
42. Fewtrell MS, Morley R, Abbott RA, et al. Double-blind, randomised trial of long-chain polyunsaturated fatty acids in formula fed to preterm infants. Pediatrics. 2002;110:73–82.
43. Fewtrell MS, Abbott RA, Kennedy K, et al. Randomized, double-blind trial of long-chain polyunsaturated fatty acid supplementation with fish oil and borage oil in preterm infants. J Pediatr. 2004;144:471–9.
44. Clandinin MT, Van Aerde JE, Merkel KL, Harris CL, et al. Growth and development of preterm infants fed infant formulas containing docosahexaenoic acid and arachidonic acid. J Pediatr. 2005;146(4):461–8.
45. Schulzke SM, Patole SK, Simmer K. Long chain polyunsaturated fatty acid supplementation in preterm infants. Cochrane Database Syst Rev. 2011;(2):CD000375.
46. Beyerlein A, Hadders-Algra M, Kennedy K, et al. Infant formula supplementation with long-chain polyunsaturated fatty acids has no effect on Bayley developmental scores at 18 months of age–IPD meta-analysis of 4 large clinical trials. J Pediatr Gastroenterol Nutr. 2010;50(1):79–84.
47. Lapillonne A, Carlson SE. Polyunsaturated fatty acids and infant growth. Lipids. 2001;36(9):901–11.
48. Carlson SE, Cooke RJ, Werkman SH, Tolley EA. First year growth of infants fed standard formula compared with marine oil supplemented formula. Lipids. 1992;27:901–7.
49. Rosenfeld E, Beyerlein A, Hadders-Algra M, et al. IPD meta-analysis shows no effect of LC-PUFA supplementation on infant growth at 18 months. Acta Paediatr. 2009;98(1):91–7.

50. Henriksen C, Haugholt K, Lindgren M, et al. Improved cognitive development among preterm infants attributable to early supplementation of human milk with docosahexaenoic acid and arachidonic acid. Pediatrics. 2008;121(6):1137–45.
51. Makrides M, Gibson RA, McPhee AJ. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. JAMA. 2010;304(15):1675–83.
52. Fleith M. Clandinin MT Dietary PUFA for preterm and term infants: review of clinical studies. Crit Rev Food Sci Nutr. 2005;45(3):205–29.
53. Lapillonne A, Jensen CL. Reevaluation of the DHA requirement for the premature infant. Prostaglandins Leukot Essent Fatty Acids. 2009;81(2–3):143–50.
54. Drenckpohl D, McConnell C, Gaffney S, et al. Randomized trial of very low birth weight infants receiving higher rates of infusion of intravenous fat emulsions during the first week of life. Pediatrics. 2008;122:743–51.

Chapter 24
Dietary Management of Hypercholesterolemia in Infants and Children

Corina Hartman and Raanan Shamir

Key Points

- Studies have shown that atherogenesis early in life is associated with the traditional risk factors for CAD
- Many lifestyle changes are difficult to achieve in adulthood and even harder to maintain over the long term, it seems reasonable to attempt to alter these risk factors early in life
- Lifestyle modification is the mainstay of treatment, sometimes it is not sufficient to achieve the desired cholesterol levels and drug therapy may be warranted
- With the increasing use of drugs in the treatment of children with hypercholesterolemia, it must be emphasized that dietary and drug treatments are synergistic and dietary and lifestyle modifications must not be abandoned after the initiation of drug therapy

Keywords Hypercholestrolemia in children • Exercise • Coronary artery disease • Omega-3 fatty acids • Caloric intake

Introduction

Coronary artery disease (CAD) continues to be the single leading cause of mortality in Europe and United States and a major cause of morbidity [1]. The Framingham cohort and subsequent studies have identified male gender, blood cholesterol, blood pressure, diabetes, and smoking status as the major risk factors for CAD [2]. All CVD risk factors, including abnormal lipid levels, often emerge during childhood and adolescence [3]. The prevalence of lipid abnormalities in children is increasing, primarily in association with the concomitant epidemic of obesity and the metabolic syndrome. The National Health and Nutrition Examination Survey (NHANES) for 1999–2006 found that the prevalence of abnormal lipid levels defined as low-density lipoprotein cholesterol (LDL-C) ≥130 mg/dL, low high-density lipoprotein cholesterol (HDL-C)≤ 35 mg/dL, and high triglyceride levels ≥150 mg/dL, among youths aged 12–19 years was 20.3%. This prevalence varied by body mass

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Table 24.1 Lipid profile for children 2–18 years old according to NCEP guidelines (lipid Research clinic pediatric prevalence study) [18]

	Acceptable (mg/dL)	Borderline(mg/dL)	Elevated (mg/dL)
Lipoproteins	<75th percentile	75th–95th percentile	>95th percentile
Total cholesterol	<170	170–199	>200
LDL-cholesterol	<110	110–129	>130
HDL-cholesterol	>45		
Triglycerides	<100	100–124	>125

index (BMI); 14.2% of normal weight but 22.3% of overweight and 42.9% of obese had at least one abnormal lipid level [4]. Furthermore, elevated non-HDL-C concentrations during childhood and adolescence also have been shown to predict high non-HDL-C concentration during adulthood; for example, a non-HDL-C concentration above the 95th percentile during childhood was found to be 86–96% sensitive and 96–98% specific in predicting an elevated LDL-cholesterol concentration during adulthood [5].

The presence of multiple cardiovascular risk factors is associated with early acceleration of atherosclerosis [6]. Early atherosclerotic lesions in children, adolescents, and young adults who died in accidents, have been shown to be significantly related to higher antecedent levels of total cholesterol (TC) and LDL-C, lower levels of HDL-C, and other cardiovascular disease (CVD) risk factors, such as obesity, higher blood pressure levels, and cigarette smoking [6–8]. Four major prospective epidemiological studies from Muscatine [9], Bogalusa [10], the Coronary Artery Risk Development in Young Adults (CARDIA) [11], and the Pathobiological Determinants of Atherosclerosis in Youths (PDAY) [12] showed that CVD risk factors in children and adolescents, particularly LDL-C and obesity, predicted clinical manifestations of atherosclerosis in young adults, as judged by carotid intima medial thickness (IMT), coronary artery calcium, or brachial flow-mediated dilatation.

Based on the NCEP report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents, the American Academy of Pediatrics (AAP) recommend selective screening for children and adolescents in the following high-risk group: (1) children with undiagnosed monogenic dyslipidemia such as familial hypercholesterolemia (FH) (family history of premature CHD or at least one parent with a high TC level ,TC ≥ 240 mg/dL) or whom family history is unknown and other risk factors are present; (2) those with undiagnosed secondary causes of dyslipidemia (endocrine, genetic, metabolic, renal or liver disorders); and (3) those with multifactorial dyslipidemia (polygenetic or related to risk factors, such as overweight, hypertension, diabetes mellitus) [13, 14]. The AAP recommendations are in agreement with the American College of Obstetricians and Gynecologists for screening in adolescents and the American Heart Association (AHA) from 2003, updated in 2007 [15, 16]. However, the National Lipid Association recommended at its last Annual Scientific Session from May 2011, universal screening for children 9–11 years old and selective screening, starting from age 2 in children with CAD risk factors [17].

The recommended screening tests for targeted population are fasting lipids in children >2 years of age. The NCEP recommended levels for identifying children and adolescents with abnormal lipid and lipoprotein concentration are based on Lipid Research Clinic Pediatric Prevalence Study data and are the same for all children from 2 to 18 years of age (Table 24.1) [18]. Recently, data from the NHANES 1988–2002 were used to develop age- and gender-specific thresholds that can be used to denote abnormal levels of TC, LCL-C, HDL-C, and triglycerides for 12–20 years old [19].

The lipid-linked cardiovascular risk is principally determined by the concentrations of LDL-C, and of HDL-C (inversely), as concentrations of blood TC and LDL-C increase so does the risk of cardiovascular disease (CVD) [20]. This makes the LDL-C the preferred target for lipid-lowering interventions. Systematic reviews and meta-analyses in adults have shown that lowering of cholesterol whether by diet, drugs, or other means, decreases CVD risk [19].

The first formal institutional recommendation on risk factors in children came from the Committee on Nutrition of the AAP in 1972 and focused on diet as a means of controlling plasma cholesterol levels in children with FH [21]. The AHA made a similar recommendation in 1978 and expanded the application to all types of dyslipidemia [22]. The current treatment strategies have been laid out in the comprehensive report of the 1992 NCEP Expert Panel on Children and Adolescents and although dates almost two decades ago, these guidelines are still the basis for the present recommendations of AAP and AHA, with therapeutic lifestyle changes, including dietary modification, physical activity and weight control as the first line of treatment for all childhood dyslipidemia [23, 24].

Diet and Hypercholesterolemia, the Evidence

Lipid-enriched diets are often used to induce or accelerate the rate of atherosclerotis progression in murine models of atherosclerosis. By far, the most widely used high-fat diet for atherosclerosis experiments is the so-called Western-type diet, which contains 21% fat and 0.15% cholesterol [25]. As for the opposite, regression of preexisting atherosclerotic lesions has also been demonstrated in mice models of atherosclerosis after switching to a chow diet [26]. In monkeys with severe atherosclerosis, regression of atherosclerosis occurred when blood cholesterol level was lowered with diet and drugs [27].

Epidemiological studies have shown that, in humans, the major nutritional determinant of differences in serum cholesterol levels between countries appears to be the proportion of saturated fat in the diet. This was also observed in pediatric populations [28]. On an individual basis, changes in TC and LDL-C blood levels can be predicted by changes in the various fatty acids, again with the largest effect contributed to saturated fatty acids [29]. Total blood cholesterol levels in children vary geographically. In countries such as the Philippines, Italy, and Ghana where saturated fat constitutes approximately 10% of the dietary intake, the serum cholesterol levels in boys 8–9 years of age are generally below 160 mg/dL. In boys from countries such as the Netherlands, Finland, and the United States, the saturated fat intake varies from 13.5% to 17.7% of energy intake, and serum cholesterol levels are generally around 160 mg/dL [29].

Dietary Intervention, Human Studies

The principal goal of dietary treatment of hypercholesterolemia is the reduction of the plasma LDL-C. This is best accomplished by enhancing the activity of LDL receptors and, at the same time, depressing liver synthesis of cholesterol. Both cholesterol and saturated fat down-regulate the LDL receptor and inhibit the removal of LDL from the plasma by the liver. Saturated fat down-regulates the LDL receptor, especially when cholesterol is concurrently present in the diet. The total amount of dietary fat is also important. The greater the flux of chylomicron remnants into the liver, the greater is the influx of cholesterol ester. In addition, factors that affect LDL synthesis could be important. These include excessive calories (obesity) that enhance very low-density lipoprotein (VLDL) and, hence, LDL synthesis, mono- and polyunsaturated fatty acids. Therefore, the optimal, classic diet for treatment of children and adults has the following characteristics: low fat (25–35% kcal), saturated fat (<7% kcal) and cholesterol (<200 mg) and replacement with fat from omega-6 polyunsaturated and monounsaturated fat, carbohydrate (55–65% kcal), and protein (15–25% kcal).

Low-saturated fat, low-cholesterol diets in adults have been shown to lower LDL-C by an average of 12%, with a 1.9-mg/dL decline in LDL-C for every 1% decline in saturated fat [30]. Further

restricting saturated fat from 10% of total energy to 7% (the Therapeutic Lifestyle Change diet) increased the LDL-C reduction to 16%. Adult studies have shown that, depending on age, reduction of cholesterol levels by 10%, decrease the incidence of CAD by 54% at age 40 years, 39% at age 50, 27% at 60, 20% at 70, and 19% at 80 [20].

The Cardiovascular Disease in the Young Council of the AHA has recommended since 1983 reduction of dietary fat and salt for all children to control serum lipids and blood pressure. These recommendations were echoed by the American Academy of Pediatrics in 1986 and the NCEP in 1992 [31, 32].

Pediatric studies confirmed the results of the adult reports showing safety and efficacy of a low-cholesterol and low-saturated fat diet, at both clinical and school-based levels. In 1972, teenage boys in a New England boarding school lowered their mean serum cholesterol concentration (14%) after consuming a fat-modified diet [33]. A fat-modified diet produced a nearly identical result in Finnish children 8–18 years of age in 1986. Intensive intervention in schools to change diet among 13- to 15-year-old adolescents reduced serum cholesterol levels by 0.5 mmol/L (19 mg/dL) [34].

The Dietary Intervention Study in Children (DISC) is a controlled trial started in 1987 and conducted over 3 years in U.S. children, 8–11 years old with high LDL-C (80th–90th percentile). The children were randomized to an intervention group ($n=334$) receiving a diet with 28% of energy from total fat, 8% from saturated fat, up to 9% from polyunsaturated fat, and less than 75 mg cholesterol per 1,000 kcal per day and to a control group on regular care ($n=329$) that consumed 33–34% of calories as total fat, 12.7% of calories as saturated fat, and 112 mg per day of cholesterol. Reductions in dietary total fat, saturated fat, and cholesterol were greater in the intervention than in the usual care group throughout the intervention period. At 1 year, 3 years, 5 years and at the last visit (7.5 years), the intervention compared with the usual care group had 4.8 mg/dL, 3.3 mg/dL, 2.8 mg/dL and 2.0 mg/dL lower LDL-C ($P<0.001$ and $P < .02$), at 1 and 3 years, but not at 5 years ($P=0.11$) or at the last visit ($P=0.25$) respectively. There were no differences at any data collection point in sexual maturation, height or BMI. In conclusion, dietary fat modification can be achieved and safely sustained in actively growing children with elevated LDL-C and elevated LDL-C levels can be improved significantly up to 3 years, but not sustained in time [35, 36].

In the Special Turku Coronary Risk Factor Intervention Project (STRIP), a low-saturated fat, low-cholesterol diet was introduced to healthy infants in the intervention group ($n=540$) begun at weaning (age 7 months) with parental dietary education continued through the age of 7 years. The intervention was individualized for each child and aimed at achieving a fat intake of 30–35% of daily energy, with a ratio of saturated to monounsaturated plus polyunsaturated fatty acid of 1:2 and cholesterol intake <200 mg/dL. The control children ($n=522$) received the basic health education routinely given at Finnish well-baby clinics and through school health care. A low-saturated fat, low-cholesterol-oriented nutrition intervention had a favorable effect on saturated fat intake and serum total and LDL-C concentrations throughout the first 14 years of life. Boys had lower total and LDL-C concentrations than girls throughout childhood ($P<0.001$), and the intervention effect on serum cholesterol concentration was larger in boys than girls. The two study groups showed no difference in growth, BMI, pubertal development, or age at menarche (median, 13.0 and 12.8 years in the intervention and control girls, respectively; $P<0.52$), indicating that a low-fat diet may be instituted safely and effectively after 6 months of age under medical supervision [37–40].

An additional study, the Parent–child AutoTutorial (PCAT) program reported 8% improvement in LDL-C level compared with the at-risk control group ($P<0.05$). The studies that address dietary interventions in general populations of children and adolescents are presented in (Table 24.2 [41].

In conclusion, trials of dietary intervention have shown that the low-fat, low-cholesterol diet recommended by the National Cholesterol Education Program in 1992 report is safe and thus can be implemented in population-based strategies of cardiovascular disease risk lowering.

Table 24.2 RCT of dietary interventions for the treatment of hypercholesterolemia in children and adolescents

Reference	Intervention	Population, *N* (age)	Baseline LDL-C	Postinterventiom LDL-C	Safety/secondary end point
Obarzanek [36]	28% energy total fat <8% saturated fat <9% PUFA	Intervention $n=334$ Control $n=329$	LDL-C 80–98%	Decrease of LDL-C 1 year $P<0.001$	No change in HDL-C or TG No difference in height, weight or Tanner staging
DISC study	<75 mg/1000 kcal cholesterol per day	7.8–810.8 years		3 years $P<0.02$ 5 years $P=0.11$) 7.4 years $P=0.25$ TC similar pattern	
Niinikoski H. Circulation. 2007;116:1032 The STRIP study	Fat intake 30–35% Saturated/to monounsaturated plus polyunsaturated fatty acid of 1:2 Cholesterol <200 mg/day	Intervention, $n=540$ Control, $n=522$ From 7 months to 7 years	Random values	Decrease of LDL-C At 14 years Boys $P<0.001$ Gils $P=0.12$	No change in HDL-C No difference in growth, BMI, pubertal development, or age at menarche
Kuehl KS. Prev Med. 1993;22:154	One or four multiple 90-min sessions of family-oriented nutritional education 16 weeks	295 children 2–15 years	Hypercholesterolemia (>185 mg/dL)	Decrease of TC in both groups $P<0.0001$ LDL-C in multiple session group only $P<0.02$	No difference in growth
Gold KV. West J Med 1988;148:299	Step 1 diet for all Intervention; 38 g oat bran Control; step 1	29 children School age Mean 10 years	Hypercholesterolemia (>185 mg/dL)	TC, LDL-C, HDL-C not different apoB decrease in low fat group $P<0.005$	Decreased significantly in SFT in low-fat controls ($p=0.03$)
Shannon BM. Pediatrics 1994;94:923	Home-based, parent–child autotutorial (PCAT) dietary education	261 children 4- to 10-year-old	TC> 4.55 mmol/L Boys 2.77–4.24 mmol/L Girls 2.90–4.24 mmol/L	LDL-C decline of the PCAT $P<0.005$	Dietary knowledge of PCAT improve Saturated fat consumed by PCAT decrease
Williams CL. J Am Coll Nutr 1995;14:251	Step 1 diet vs. Step 1 with physilium	50 healthy 2 to 11 years	LDL-C >110 mg/dL	TC decrease 21 mg/dL vs 11.5 mg/dL LDL-C decrease 23 mg/dL vs. 8.5 mg/dL. HDL-C increased 4 mg/dL vs. 1 mg/dL	

(continued)

Table 24.2 (continued)

Reference	Intervention	Population, *N* (age)	Baseline LDL-C	Postinterventiom LDL-C	Safety/secondary end point
Williams CL. J Am Coll Nutr 1999;18:572	Plant stanols 3g/day cross-over study 13 weeks	19 children 2–5 years	Random	TC decrease of 19.9 mg/dL ($p<0.01$) LDL-C decrease of 14.6 mg/dL ($p<0.05$) from baseline	No change in HDL or TG
Engler [63]	1.2 g/d DHA 6 weeks	20 children 9–19 years	LDL-C >130 mg/dL	No changes in total cholesterol, LDL, HDL,	Shift of lipoprotein subclass distribution
McCrindle BW. Arch Pediatr Adolesc Med. 1998;152:1089	Garlic extract 6 weeks	30 children 8–18 years	TC >185 mg/dL	No changes in total cholesterol, LDL, HDL, and triglyceride	
Weghuber D. Br J Nutr. 2008;99:281	Soy protein 0.25-0.5 g/kg 3 months	23 children 4–18 years	LDL-C >155 mg/dL TC >270 mg/dL	Significant decrease vs. baseline TC by 7.7% ($p<0.002$) LDL-C by 6.4%($p<0.0003$)	No change in HDL or TG

Low carbohydrate diets have been proved to be effective alternatives to low-fat diets for weight loss, and have shown even more favorable effects on lipids profile and on glycemic control in overweight adults [42]. The efficacy of low carbohydrate diets in children with hypercholesterolemia is unsettled, yet. The few, so far published studies have used these diets for weight reduction in overweight children and the lipid profile was evaluated only as a secondary endpoint. The trials of Sondike et al. (RCT) and Dunlap BS (pilot) demonstrated a significant decrease in LDL-C only in the low-fat high-carbohydrate diet group [43, 44]. Other studies of low carbohydrate diets in overweight youths reported a significant decrease in TC, LDL-C and triglyceride levels, although not different to the low fat diet [45, 46].

Dietary Interventions, Recommendations

Whenever a fasting lipoprotein analysis is performed, two measurements should be made and the LDL cholesterol levels should be averaged because of intraindividual variability. Recommendations for further evaluation and treatment are then based on the averaged LDL-C value, with LDL-C levels between 2.85 and 3.34 mmol/L (110 and 129 mg/dL) defined as borderline high and those ≥3.35 mmol/L (≥130 mg/dL) defined as high [23].

The most frequent cause of monozygotic hypercholesterolemia in childhood is familial hypercholesterolemia (FH). FH is an autosomal-dominant condition resulting from deficient or defective LDL receptors and hence impaired clearance of circulating LDL particles. Other causes of inherited hypercholesterolemia with similar presentation include apoB 100 mutations, homozygous autosomal recessive hypercholesterolemia (ARH), and mutations in proprotein convertase subtilisin-like kexin type 9 (PCSK9) [47]. FH results in extreme elevations in LDL-C that may distinguish the condition from other primary and most secondary causes of hyperlipidemia. The diagnosis can usually be made clinically by the presence of highly abnormal fasting lipoprotein levels in family members, combined with a positive family history of premature CAD and events. However, genetic testing remains the criterion standard, although it is not widely available [48]. Wiegman and colleagues studied 1034 children from kindreds with FH, including assessment of LDL receptor mutations, and noted that an LDL-C level >3.5 mmol/L (>135 mg/dL) predicted the presence of FH with a 98% posttest probability, differentiating affected individuals from their unaffected family members [49].

Cholesterol-lowering therapy in children with hypercholesterolemia, including FH, starts with dietary intervention and lifestyle modification. The Scientific Statement from AHA for the treatment of high-risk lipid abnormalities in children and adolescents advocates the use of dietary treatment also as adjuvant to pharmacological treatment [16]. Existing pediatric guidelines are based on a consensus report originally published in 1992 by the NCEP Expert Panel on Blood Cholesterol Levels in Children and Adolescents [23]. The NCEP has recommended a two-level nutritional approach, which has been adopted, with some differences, by both AAP and AHA: a *population-based approach* aimed at shifting the population distribution of cholesterol levels and an *individualized approach* for high-risk group who needed further monitoring and management [14].

The cornerstone recommendation of the *population-based approach* is that all healthy children >2 years of age adopt a fat- and cholesterol-restricted diet according to the Dietary Guidelines for Americans [14]. The recent 2008 AAP guidelines place an emphasis on improving the quality of dietary fat rather than reducing total fat consumption and advocate lowering the recommended age for dietary initiation of a low-fat diet in high-risk groups [23]. Although fat-restricted diets are generally not recommended for children under 2 years of age, the AAP guidelines suggest considering the use of low-fat dairy products for high-risk children aged 1 year and older with the BMI ≥ 85th percentile or a family history of obesity, dyslipidemia, or CVD. Evidence from the ongoing STRIP study shows that the growth and neurological development of children aged 7 months and up who were maintained

Table 24.3 Recommended LDL-level for pharmacological treatment of children and adolescents [52]

Patient' characteristics	Recommended LDL-Cholesterol cut-off levels
No risk factors for CAD	LDL-C levels persistently >190 mg/dL despite intensive dietary intervention (Step 2 diet)
Positive family history for premature CAD (FH) Other risk factors: overweight, hypertension, smoking	LDL-C levels persistently >160 mg/dL despite intensive dietary intervention (Step 2 diet)
Children with diabetes mellitus, after heart transplant, heterozygous FH, coronary artery disease (aneurisms after Kawasaki disease	LDL-C levels persistently >130 mg/dL despite intensive dietary intervention (Step 2 diet)

on a low-fat diet was comparable to controls. Consumption of a wide variety of foods was recommended to achieve nutrient needs and with a goal to achieve an average daily intake of <10% of total calories from saturated fat with <30% from total fat and intake of <300 mg/d dietary cholesterol (former Step 1 diet) [50]. The general dietary recommendations of the AHA for those aged 2 years and older stress a diet that primarily relies on fruits and vegetables, whole grains, low-fat and nonfat dairy products, beans, fish, and lean meat. These general recommendations echo other recent public health dietary guidelines in emphasizing low intakes of saturated and *trans* fatty acids, cholesterol, added sugar and salt; energy intake and physical activity appropriate for the maintenance of a normal weight for height; and adequate intake of micronutrients. The recently published *Dietary Guidelines for Americans* (for those 2 years of age and older) and American Academy of Pediatrics Nutrition Handbook provide important supporting reference information with regard to overall diet composition, appropriate caloric intakes at different ages, macronutrients, micronutrients, portion size and food choices [51].

The *high-risk individual approach* recommend that, for children whose LDL-C level remains >3.35 mmol/L (>130 mg/dL) while compliant with the fat- and cholesterol-restricted diet, a more restrictive diet is implemented (former Step 2 diet) [50]. This diet further limits saturated fat intake to <7% of total caloric intake and cholesterol intake to <200 mg/d. Despite compliance with lifestyle recommendations, some high-risk children and adolescents with high LDL-C levels will require lipid-lowering drug therapy, particularly those with FH [52]. LDL-C lowering drug therapy is recommended only in those children >8 to 10 years of age whose LDL-C remains extremely elevated after an adequate 6- to 12-month trial of diet therapy (LDL-C ≥ 190mg/dL or LDL-C ≥ 160mg/dL and a family history of CAD or two or more risk factors, or LDL-C ≥ 130mg/ dL if diabetes mellitus is present) (Table 24.3).

Effect of a Low-Fat Diet in Childhood on Future CVD in Adulthood

The evidence that a low-saturated fat, low-cholesterol diet in childhood will prevent CVD in adulthood can only be inferred from epidemiological studies, where children from countries with a lower prevalence of CVD had lower TC levels than those children from countries with higher CVD and TC levels [53, 54].

Children with heterozygous FH have been shown to have abnormalities on noninvasive vascular assessments, including greater carotid-intima media thickness and abnormal arterial endothelial function [55]. These have been used as atherosclerosis surrogate markers and lipid-lowering interventions, including low-fat, low-cholesterol diets have been shown to improve these abnormalities. Evaluation of flow-mediated dilatation at 11 years in children participating in STRIP study, a low-saturated-fat diet introduced in infancy and maintained during the first decade of life, was associated with enhanced endothelial function in boys, but not in girls, effects mediated in part by the diet-induced

reduction in TC [56]. In addition, in the same Finnish study, the children showed improved insulin sensitivity at 9 years and overweight was less prevalent in the intervention (10%) compared with 19% of the control girls.

Nutritional Supplements

There has been a great deal of interest in dietary supplements and complementary medicines, although few have been subjected to rigorous clinical evaluation. Obviously, complementary medicines and dietary supplements and modifications should be supported by rigorous clinical trial evidence before being adopted as acceptable therapies for the management of hyperlipidemia in children.

Modification of dietary fat quality. In adults, the major nutritional determinant of differences in serum cholesterol levels between countries appears to be the proportion of saturated fat in the diet. In addition, there are concerns whether the fat- and cholesterol-restricted diets adversely affect HDL-C, LDL particle properties, and triglycerides blood levels. A recent study has suggested that changes in the quality of dietary fat consumption with substitution of products predominating in saturated fat for those predominating in polyunsaturated fats, without altering total fat intake, may result in an >15% reduction in LDL-C levels [57]. Dietary enrichment with rapeseed or canola oil has been shown to lower triglyceride and VLDL levels without affecting HDL [58].

Stanols. Partial substitution of dietary fat consumption with margarines high in plant stanol esters can reduce LDL-C by an additional 10–15% when added to a low-fat diet. The proposed mechanism of action of plant stanols and sterols is lowering the absorption of dietary cholesterol. Plant stanols and sterols may be added to a number of food products, including spreads and margarine, orange juice, yogurt drinks, cereal bars, and dietary supplements. A clinical trial of plant stanol ester margarine in 81 children showed that LDL-C levels were lowered by a mean of 7.5%, with good tolerance [59]. Gylling and colleagues performed a crossover trial in 15 children with FH using partial dietary fat substitution with sitostanol ester dissolved in rapeseed oil margarine. They showed that LDL-C levels were reduced by a mean of 15%, and ratios of HDL-C to LDL-C levels were improved by a mean of 27% [60]. The most important safety concern with these products is that they may also result in decreased absorption of fat-soluble vitamins and beta-carotene. Formal recommendation of their use for children awaits clinical trial data.

Soy protein. The source of dietary protein has been shown to have a significant influence on the concentrations of plasma cholesterol and lipoproteins with soy protein having hypocholesterolemic effect when compared with casein [61]. In studies on hypercholesterolemic adults, substitution of mixed animal proteins with soy-protein induced moderate to marked plasma cholesterol decreases. Small studies of dietary alterations in hyperlipidemic children have shown that substitution with soy-based protein may increase HDL-C and lower VLDL levels and triglyceride and may lower LDL-C levels [62]. At the present time, however, adjunct dietary intervention with soy protein is not advocated for patients with dyslipidemia.

Omega-3 fatty acids. Diet supplementation with ω-3 fatty acids has been advocated, but not supported by randomized controlled clinical trials. Compared with placebo, supplementation of a low-fat diet with omega-3 fatty acid, docosahexaenoic acid 1.2 g/day, did not lower LDL-C, but changed the distribution between LDL subclasses with shifts toward less dense LDL particles, 91% increase in the largest LDL and a 48% decrease in the smallest LDL subclass as compared to placebo [63].

Dietary fiber. Increased intake of soluble fiber is recommended as an adjunct to the reduced intakes of saturated fatty acids and cholesterol. Water-soluble fibers, such as psyllium, can provide an additional 5–10% lowering effect on LDL-C. The proposed mechanism of action of fibers is thought to be by binding to bile acids cholesterol and its removal from the enterohepatic circulation. Studies reporting the effect of water-soluble supplemental fibers such as psyllium have been, however, equivocal;

some have shown a slight reduction in LDL-C concentration by approximately 5–10%. Dennison and colleagues did not show any benefit on lipid levels in a crossover clinical trial in 20 hyperlipidemic children supplemented with psyllium-enriched cereal [64]. In contrast, Davidson and colleagues who performed a similar crossover clinical trial in 26 hyperlipidemic children, showed a modest LDL-C reduction of 7% with the psyllium-enriched versus control group [65].

Garlic. Garlic extract preparations have been marketed for the treatment of hyperlipidemia, although evidence of a beneficial effect on the lipid profile has not been noted in independent clinical trials. A placebo-controlled, double-blind clinical trial conducted in 30 children with familial hyperlipidemia using a commercially available garlic extract showed no clinically important effect on the lipid profile or any other cardiovascular risk factor [66].

Increased physical activity may also be useful for improving dyslipidemia in children and adolescents. Physical activity primarily affects HDL and triglyceride concentrations, but improvement of LDL-cholesterol concentration has also been documented [67]. Although there have been few randomized clinical trials to document the effects of physical activity as a specific intervention for children and adolescents, supportive data are available from epidemiological studies [67].

Nutritional Assessment and Counseling

Dietary intervention should be preceded by a detailed nutritional assessment including anthropometry and current eating patterns history. In general, dietary recommendations should be consistent with good nutrition, aimed at a proper caloric balance to ensure optimal growth and development while preventing obesity. Close guidance and follow up by a qualified dietitian should assist the child and family alike. As children begin to consume fewer calories from fat, the missing calories should be replaced by eating more grain products, fruits, vegetables, calcium-rich foods (low-fat milk products), or protein-rich foods (lean meat, poultry, fish). No single food item provides all essential nutrients thus, choosing a wide variety of food from all the food groups will ensure an adequate diet.

The home environment aids children and adolescents make the right nutritional choices and maintain a healthful diet. Parents should be encouraged to act as a role model for their children and all family members should consume a healthy diet. Dietitians should guide children and their families in making healthy choices at school, and in fast-food restaurants. Care should be taken as some parents and their children may implement an extremely low-fat diet, leading to nutritional insufficiency and subsequent growth failure [68].

Follow Up

The reduction in fat intake, if done without professional monitoring and counseling, could potentially lead to a deficiency of essential fatty acids and fat soluble vitamins and a reduction in the overall energy content of the diet which has implications for satiety and growth in children who have relatively high energy requirements [68]. An increase in the carbohydrate content of the diet may lead to raised blood levels of triglyceride.

Children and adolescents placed on a low-fat diet should have height and weight assessments every 6 months to ensure that linear growth is not compromised. To date, the exact percentage of dietary intake from fat that supports normal growth and development while maximally reducing atherosclerosis risk needs clarification, especially when the effect of carbohydrates' intake in children is ill-defined [43–46].

Safety of Dietary Therapy in Infants, Children, and Adolescents

Data from the ongoing Special Turku Risk Intervention Program (STRIP) conducted in infants as young as 7 months of age and from the DISC study conducted in children aged 8–10 years throughout adolescence have demonstrated that these dietary recommendations are safe and do not interfere with normal growth, development, and sexual maturation [69, 70]. Failure to thrive, however, has been demonstrated in children under 2 years of age who eat fat-restricted, low energy diets. Thus, implementation of these diets should be very carefully supervised in children in this age group. Growth failure was reported in one study in eight (20%) of 40 children with dyslipidemia, 3 (7.5%) of whom had nutritional dwarfing and no progression of puberty [71]. In that study, families were unsupervised in the implementation of low-fat, low-cholesterol diets for a period up to 4.5 years; those with nutritional dwarfing had longer periods of time between diagnosis and formal dietary assessment and counseling. In addition, in some studies, there were lower intakes of calcium, zinc, vitamin E, and phosphorus on low-fat diets [72].

Therefore, although normal growth could be achieved and maintained on low-fat diets, attention needs to be paid to ensure adequate intake of these key nutritional elements. Medical and nutritional support is necessary to reinforce good dietary behaviors and ensure nutritional adequacy [73, 74].

Lastly, people with hypercholesterolemia may be susceptible to potentially detrimental psychological and nutritional consequences of their dietary treatment. However, so far, few studies have assessed the quality of life of children with dyslipidemia on dietary intervention [75].

Summary of Recommendations for Screening and Treatment of Dyslipidemia in Children and Adolescents

- All healthy children >2 years of age should adopt a fat- and cholesterol-restricted diet according to the Dietary Guidelines for Americans.
- Fasting serum lipid profiles should be performed in a selected group of children older than 2 years, preferably before 10 years and including: (1) children with a family history of dyslipidemia or premature CAD, (2) children with disorders associated with secondary dyslipidemia, and (3) children affected by risk factors, i.e., overweight, hypertension, diabetes mellitus.
- For children whose LDL-C level remains >3.35 mmol/L (>130 mg/dL) while compliant with the fat- and cholesterol-restricted diet, a more restrictive diet should be implemented. This diet further limits saturated fat intake to <7% of total caloric intake and cholesterol intake to <200 mg/d.
- Close guidance and follow up by a qualified dietitian should be to assist the child and family constantly.
- LDL-C lowering drug therapy is recommended only in those children >8 to 10 years of age, who after an adequate 6- to 12-month trial of diet therapy still have extremely high LDL-C levels.

Dietary and Lifestyle Interventions, Summary of AHA and AAP Recommendations

- Adequate nutrition should be achieved by eating a wide variety of foods
- Total caloric intake should be sufficient to support normal growth and development and maintain/achieve appropriate body weight
- No decrease in total protein is recommended

- Total fat should provide no more than 30% but no less than 25% of total calories
- In children aged 12 months to 2 years who are overweight, obese, or have a family history of obesity, dyslipidemia, or cardiovascular disease the use of reduced-fat milk/dairy products deserve careful consideration
- Saturated fat should provide less than 10% of total calories for all children and less than 7% for children in high-risk groups
- Eliminate *trans*-fat and replace them with polyunsaturated fat, and include fish, especially oily fish (at least twice a week)
- Children should consume no more than 100mg/1000 cal of cholesterol per day and less than 75 mg/1000 cal cholesterol per day if they belong to the high-risk group
- Children should consume at least 5 serving of vegetable and fruits and whole grain bread/cereals and simple sugars should be replaced with complex carbohydrates
- All children should eat adequate amounts of dietary fiber (age+5 g/ day) up to 20 g
- Reduce salt intake, including salt from processed food
- The diet should be implemented under counseling and monitoring of a nutritionist (physician or a dietitian)
- Physical activity (time spent in active play) should be at least 1 h/ day, whereas screen time (television, computer, or video game) should not exceed 2 h/day

Conclusions

The progression of atherosclerosis from childhood fatty streaks to clinically significant fibrous plaques during young adulthood was established in the 1980s by the publication of postmortem studies from the Bogalusa Heart Study and the PDAY study. These studies have shown that atherogenesis early in life is associated with the traditional risk factors for CAD and that these risk factors tend to track into adulthood. Since many lifestyle changes are difficult to achieve in adulthood and even harder to maintain over the long term, it seems reasonable to attempt to alter these risk factors early in life.

While lifestyle modification is the mainstay of treatment, sometimes it is not sufficient to achieve the desired cholesterol levels and drug therapy may be warranted. Nevertheless, with the increasing use of drugs in the treatment of children with hypercholesterolemia, it must be emphasized that dietary and drug treatments are synergistic and dietary and lifestyle modifications must not be abandoned after the initiation of drug therapy.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2011 update: a report from the American Heart Association. Circulation. 2011;123:e18–209.
2. Kannel WB, McGee DL. Composite scoring–methods and predictive validity: insights from the Framingham Study. Health Serv Res. 1987;22:499–535.
3. Ford ES, Mokdad AH, Ajani UA. Trends in risk factors for cardiovascular disease among children and adolescents in the United States. Pediatrics. 2004;114:1534–44.
4. Centers for Disease Control and Prevention. Prevalence of abnormal lipid levels among youths, United States, 1999–2006. MMWR Morb Mortal Wkly Rep. 2010;59:29–33.
5. Srinivasan SR, Myers L, Berenson GS. Distribution and correlates of non-high-density lipoprotein cholesterol in children: the Bogalusa Heart Study. Pediatrics. 2002;110:e29.
6. Berenson GS, Srinivasan SR, Bao W, Newman III WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med. 1998;338:1650–6.

7. McGill Jr HC, McMahan CA, Zieske AW, Sloop GD, Walcott JV, Troxclair DA, et al. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Arterioscler Thromb Vasc Biol. 2000;20:1998–2004.
8. Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking: a preliminary report from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. JAMA 1990;264:3018–24.
9. Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: the Muscatine Study. Circulation. 2001;104:2815–9.
10. Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM, Berenson GS. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. JAMA. 2003;290:2271–6.
11. Polak JF, Person SD, Wei GS, Godreau A, Jacobs Jr DR, Harrington A, Sidney S, O'Leary DH. Segment-specific associations of carotid intima-media thickness with cardiovascular risk factors: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Stroke. 2010;41:9–15.
12. Gidding SS, McMahan CA, McGill HC, Colangelo LA, Schreiner PJ, Williams OD, Liu K. Prediction of coronary artery calcium in young adults using the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) risk score: the CARDIA study. Arch Intern Med. 2006;166:2341–7. Juonala M, Viikari JS, Laitinen T, Marniemi J, Helenius H, Rönnemaa T, Raitakari OT. Interrelations be 6.
13. Haney EM, Huffman LH, Bougatsos C, Freeman M, Steiner RD, Nelson HD. Screening and treatment for lipid disorders in children and adolescents: systematic evidence review for the US Preventive Services Task Force. Pediatrics. 2007;120:e189–214.
14. American Academy of Pediatrics. National cholesterol education program: report of the expert panel on blood cholesterol levels in children and adolescents. Pediatrics. 1992;89:525–84.
15. American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women. ACOG Committee Opinion No. 470: challenges for overweight and obese urban women. Obstet Gynecol. 2010;116:1011–4.
16. McCrindle BW, Urbina EM, Dennison BA, Jacobson MS, Steinberger J, Rocchini AP, Hayman LL, Daniels SR, American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee; American Heart Association Council of Cardiovascular Disease in the Young; American Heart Association Council on Cardiovascular Nursing. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. Circulation. 2007;115:1948–67.
17. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, Daniels SR, Gidding SS, de Ferranti SD, Ito MK, McGowan MP, Moriarty PM, Cromwell WC, Ross JL, Ziajka PE. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5:133–40.
18. Tamir I, Heiss G, Glueck CJ, Christensen B, Kwiterovich P, Rifkind B. Lipid and lipoprotein distributions in white children ages 6–19 yrs: the lipid research clinics program prevalence study. J Chronic Dis. 1981;34:27–39.
19. Courtney JJ, Janssen I. Distribution of lipoproteins by age and gender in adolescents. Circulation. 2006;114:1056–62.
20. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischemic heart disease? BMJ. 1994;308(6925):367–72.
21. American Academy of Pediatrics. Committee on nutrition: childhood diet and coronary heart disease. Pediatrics. 1972;49:305–7.
22. Glueck CJ, McGill Jr HC, Shank RE, Lauer RM. Value and safety of diet modification to control hyperlipidemia in childhood and adolescence. A statement for physicians. Ad Hoc Committee of the Steering Committee for Medical and Community Program of the American Heart Association. Circulation. 1978;58:381A–5.
23. Daniels SR, Greer FR. Committee on nutrition. Lipid screening and cardiovascular health in childhood. Pediatrics. 2008;122:198–208.
24. Gidding SS, Dennison BA, Birch LL, Daniels SR, Gilman MW, Lichtenstein AH, Rattay KT, Steinberger J, Stettler N, Van HL, American Heart Association, American Academy of Pediatrics. Dietary recommendations for children and adolescents: a guide for practitioners: consensus statement from the American Heart Association. Circulation. 2005;112:2061–75.
25. Powell-Braxton L, Veniant M, Latvala RD, Hirano KI, Won WB, Ross J, Dybdal N, Zlot CH, Young SG, Davidson NO. A mouse model of human familial hypercholesterolemia: markedly elevated low density lipoprotein cholesterol levels and severe atherosclerosis on a low-fat chow diet. Nat Med. 1998;4:934–8.
26. Raffai RL, Loeb SM, Weisgraber KH. Apolipoprotein E promotes the regression of atherosclerosis independently of lowering plasma cholesterol levels. Arterioscler Thromb Vasc Biol. 2005;25:436–41.
27. Malinow MR. Experimental models of atherosclerosis regression. Atherosclerosis. 1983;48:105–18.
28. Hunter JE, Zhang J, Kris-Etherton PM. Cardiovascular disease risk of dietary stearic acid compared with trans, other saturated, and unsaturated fatty acids: a systematic review. Am J Clin Nutr. 2010;91:46–63.

29. Müller H, Kirkhus B, Pedersen JI. Serum cholesterol predictive equations with special emphasis on trans and saturated fatty acids. an analysis from designed controlled studies. Lipids. 2001;36:783–91.
30. Kris-Etherton PM, Krummel D, Russell ME, Dreon D, Mackey S, Borchers J, Wood PD. The effect of diet on plasma lipids, lipoproteins, and coronary heart disease. J Am Diet Assoc. 1988;88:1373–400.
31. AHA Committee Report. Diet in the healthy child. Circulation. 1983;67:1411A–4.
32. American Academy of Pediatrics Committee on Nutrition. Prudent life-style for children: dietary fat and cholesterol. Pediatrics. 1986;78:521–5.
33. Stein EA, Mendelsohn D, Fleming M, Barnard GD, Carter KJ, du Toit PS, Hansen JD, Bersohn I. Lowering of plasma cholesterol levels in free-living adolescent males; use of natural and synthetic polyunsaturated foods to provide balanced fat diets. Am J Clin Nutr. 1975;28:1204–16.
34. Pesonen E, Viikari J, Akerblom HK, Räsänen L, Louhivuori K, Sarna S. Effects of dietary fat modifications on serum lipids and blood pressure in children. Circulation. 1986;73:1119–26.
35. Writing Group for the DISC Collaborative Research Group. Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol: the Dietary Intervention Study in Children (DISC): the Writing Group for the DISC Collaborative Research Group. JAMA 1995;273:1429–35.
36. Obarzanek E, Kimm SY, Barton BA, Van Horn LL, Kwiterovich Jr PO, Simons-Morton DG, Hunsberger SA, Lasser NL, Robson AM, Franklin Jr FA, Lauer RM, Stevens VJ, Friedman LA, Dorgan JF, Greenlick MR, for the DISC Collaborative Research Group. Long-term safety and efficacy of a cholesterol-lowering diet in children with elevated low-density lipoprotein cholesterol: seven-year results of the Dietary Intervention Study in Children (DISC). Pediatrics. 2001;107:256–64.
37. Niinikoski H, Viikari J, Ronnemaa T, Lapinleimu H, Jokinen E, Salo P, Seppanen R, Leino A, Tuominen J, Valimaki I, Simell O. Prospective randomized trial of low-saturated-fat, low-cholesterol diet during the first 3 years of life: the STRIP baby project. Circulation. 1996;94:1386–93.
38. Rask-Nissila L, Jokinen E, Ronnemaa T, Viikari J, Tammi A, Niinikoski H, Seppanen R, Tuominen J, Simell O. Prospective, randomized, infancy-onset trial of the effects of a low-saturated-fat, low-cholesterol diet on serum lipids and lipoproteins before school age: the Special Turku Coronary Risk Factor Intervention Project (STRIP). Circulation. 2000;102:1477–83.
39. Kaitosaari T, Ronnemaa T, Raitakari O, Talvia S, Kallio K, Volanen I, Leino A, Jokinen E, Valimaki I, Viikari J, Simell O. Effect of 7-year infancy-onset dietary intervention on serum lipoproteins and lipoprotein subclasses in healthy children in the prospective, randomized Special Turku Coronary Risk Factor Intervention Project for Children (STRIP) study. Circulation. 2003;108:672–7.
40. Talvia S, Lagstrom H, Rasanen M, Salminen M, Rasanen L, Salo P, Viikari J, Ronnemaa T, Jokinen E, Vahlberg T, Simell O. A randomized intervention since infancy to reduce intake of saturated fat: calorie (energy) and nutrient intakes up to the age of 10 years in the Special Turku Coronary Risk Factor Intervention Project. Arch Pediatr Adolesc Med. 2004;158:41–7.
41. Shannon BM, Tershakovec AM, Martel JK, Achterberg CL, Cortner JA. Reduction of elevated LDL-cholesterol levels of 4-to 10-year-old children through home-based dietary education. Pediatrics. 1994;94:923–7.
42. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, Golan R, Fraser D, Bolotin A, Vardi H, et al. Weight loss with a low-carbohydrate, mediterranean, or low-fat diet. N Engl J Med. 2008;359:229–41.
43. Sondike SB, Copperman N, Jacobson MS. Effects of a low carbohydrate diet on weight loss and cardiovascular risk factors in overweight adolescents. J Pediatr. 2003;142:253–8.
44. Dunlap BS, Bailes Jr JR. Unlimited energy, restricted carbohydrate diet improves lipid parameters in obese children. Metab Syndr Relat Disord. 2008;6:32–6.
45. Demol S, Yackobovitch-Gavan M, Shalitin S, Nagelberg N, Gillon-Keren M, Phillip M. Low-carbohydrate (low & high-fat) versus high-carbohydrate low-fat diets the treatment of obesity in adolescents. Acta Paediatr. 2009;98:346–51.
46. Bailes JR, Strow MT, Werthammer J, McGinnis RA, Elitsur Y. Effect of low-carbohydrate, unlimited calorie diet on the treatment of childhood obesity: a prospective controlled study. Metab Syndr Relat Disord. 2003;1:221–5.
47. Soutar AK, Naoumova RP. Mechanisms of disease: genetic causes of familial hypercholesterolemia. Nat Clin Pract Cardiovasc Med. 2007;4:214–25.
48. Marks D, Thorogood M, Neil HA, Humphries SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis. 2003;168:1–14.
49. Wiegman A, Rodenburg J, de Jongh S, Defesche JC, Bakker HD, Kastelein JJ, Sijbrands EJ. Family history and cardiovascular risk in familial hypercholesterolemia: data in more than 1000 children. Circulation. 2003;107:1473–8.
50. American Heart Association. Step I, step II and TLC diets. http://www.americanheart.org/presenter.jhtml?identifier_4764.
51. US Department of Agriculture and US Department of Health and Human Services. Report of the Dietary Guidelines Advisory Committee on the dietary guidelines for Americans, 2010. http://www.cnpp.usda.gov/DGAs2010-DGACReport.htm. Accessed 15 Jun 2010.

52. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, Parekh RS, Steinberger J; American Heart Association Expert Panel on Population and Prevention Science; American Heart Association Council on Cardiovascular Disease in the Young; American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Nutrition, Physical Activity and Metabolism; American Heart Association Council on High Blood Pressure Research; American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on the Kidney in Heart Disease; Interdisciplinary Working Group on Quality of Care and Outcomes Research. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, Parekh RS, Steinberger J; American Heart Association Expert Panel on Population and Prevention Science; American Heart Association Council on Cardiovascular Disease in the Young; American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Nutrition, Physical Activity and Metabolism; American Heart Association Council on High Blood Pressure Research; American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on the Kidney in Heart Disease; Interdisciplinary Working Group on Quality of Care and Outcomes Research. Circulation. 2006;114:2710–38.
53. Artaud-Wild SM, Connor SL, Sexton G, Conner WE. Differences in coronary mortality can be explained by differences in cholesterol and saturated fat intakes in 40 countries but not in France and Finland. Circulation. 1993;88:2771–9.
54. Caggiula AW, Mustad VA. Effects of dietary fat and fatty acids on coronary artery disease risk and total and lipoprotein cholesterol concentrations: epidemiologic studies. Am J Clin Nutr. 1997;65(5 Suppl):1597S–610.
55. Groner JA, Joshi M, Bauer JA. Pediatric precursors of adult cardiovascular disease: noninvasive assessment of early vascular changes in children and adolescents. Pediatrics. 2006;118:1683–91.
56. Raitakari OT, Ronnemaa T, Jarvisalo MJ, Kaitosaari T, Volanen I, Kallio K, Lagstrom H, Jokinen E, Niinikoski H, Viikari JS, Simell O. Endothelial function in healthy 11-year-old children after dietary intervention with onset in infancy: the Special Turku Coronary Risk Factor Intervention Project for children (STRIP). Circulation. 2005;112:3786–94.
57. Vartiainen E, Puska P, Pietinen P, Nissinen A, Leino U, Uusitalo U. Effects of dietary fat modifications on serum lipids and blood pressure in children. Acta Paediatr Scand. 1986;75:396–401.
58. Gulesserian T, Widhalm K. Effect of a rapeseed oil substituting diet on serum lipids and lipoproteins in children and adolescents with familial hypercholesterolemia. J Am Coll Nutr. 2002;21:103–8.
59. Tammi A, Ronnemaa T, Gylling H, Rask-Nissila L, Viikari J, Tuominen J, Pulkki K, Simell O. Plant stanol ester margarine lowers serum total and low-density lipoprotein cholesterol concentrations of healthy children: the STRIP project: Special Turku Coronary Risk Factors Intervention Project. J Pediatr. 2000;136:503–10.
60. Gylling H, Siimes MA, Miettinen TA. Sitostanol ester margarine in dietary treatment of children with familial hypercholesterolemia. J Lipid Res. 1995;36:1807–12.
61. Laurin D, Jacques H, Moorjani S, Steinke FH, Gagne C, Brun D, Lupien PJ. Effects of a soy-protein beverage on plasma lipoproteins in children with familial hypercholesterolemia. Am J Clin Nutr. 1991;54:98–103.
62. Widhalm K, Brazda G, Schneider B, Kohl S. Effect of soy protein diet versus standard low fat, low cholesterol diet on lipid and lipoprotein levels in children with familial or polygenic hypercholesterolemia. J Pediatr. 1993;123:30–4.
63. Engler MM, Engler MB, Malloy MJ, Paul SM, Kulkarni KR, Mietus-Snyder ML. Effect of docosahexaenoic acid on lipoprotein subclasses in hyperlipidemic children (the EARLY study). Am J Cardiol. 2005;95:869–71.
64. Dennison BA, Levine DM. Randomized, double-blind, placebo-controlled, two-period crossover clinical trial of psyllium fiber in children with hypercholesterolemia. J Pediatr. 1993;123:24–9.
65. Davidson MH, Dugan LD, Burns JH, Sugimoto D, Story K, Drennan K. A psyllium-enriched cereal for the treatment of hypercholesterolemia in children: a controlled, double-blind, crossover study. Am J Clin Nutr. 1996;63:96–102.
66. McCrindle BW, Helden E, Conner WT. Garlic extract therapy in children with hypercholesterolemia. Arch Pediatr Adolesc Med. 1998;152:1089–94.
67. Tolfrey K, Jones AM, Campbell IG. The effect of aerobic exercise training on the lipid-lipoprotein profile of children and adolescents. Sports Med. 2000;29:99–112.
68. Pugliese MT, Weyman-Daum M, Moses N, Lifshitz F. Parental health beliefs: a cause of non-organic failure to thrive. Pediatrics. 1987;80:175–81.
69. Lagström H, Seppänen R, Jokinen E, Niinikoski H, Rönnemaa T, Viikari J, Simell O. Influence of dietary fat on the nutrient intake and growth of children from 1 to 5 year of age: the Special Turku Coronary Risk Factor Intervention Project. Am J Clin Nutr. 1999;69:516–23.
70. Niinikoski H, Lapinleimu H, Viikari J, Rönnemaa T, Jokinen E, Seppänen R, Terho P, Tuominen J, Välimäki I, Simell O. Growth until 3 years of age in a prospective, randomized trial of a diet with reduced saturated fat and cholesterol. Pediatrics. 1997;99:687–94.
71. Lifshitz F, Moses N. Growth failure. A complication of dietary treatment of hypercholesterolemia. Am J Dis Child. 1989;143:537–42.
72. Clauss SB, Kwiterovich PO. Long-term safety and efficacy of low-fat diets in children and adolescents. Minerva Pediatr. 2002;54:305–13.

73. Hansen D, Michaelsen KF, Skovby F. Growth during treatment of familial hypercholesterolemia. Acta Paediatr. 1992;81:1023–5.
74. Kaistha A, Deckelbaum RJ, Starc TJ, Couch SC. Overrestriction of dietary fat intake before formal nutritional counseling in children with hyperlipidemia. Arch Pediatr Adolesc Med. 2001;155:1225–30.
75. Tonstad S, Novik TS, Vandvik IH. Psychosocial function during treatment for familial hypercholesterolemia. Pediatrics. 1996;98:249–55.

Chapter 25
Adipose Tissue, Its Hormones and Infant Development

Mauro Bozzola and Cristina Meazza

Keypoints

- Adipose tissue is an endocrine organ, secreting bioactive molecules which act at both the local and systemic level.
- Adiponectin is specifically expressed in subcutaneous adipose tissue and shows a protective role in the development of obesity-related disorders and metabolic syndrome.
- Leptin is principally secreted by subcutaneous adipose tissue and their circulating levels are closely associated with the amount of fat mass.
- The development of adipose tissue is very important in the first years of life, since pathogenetic mechanisms of obesity start very early in life.
- Epidemiological studies have shown an association between a reduced size at birth and increased long-term risk for obesity, insulin resistance, type 2 diabetes, hypertension and cardiovascular disease in adulthood.
- The catch-up growth in babies born with low birth weight promotes excess adiposity in relation to muscle mass, which in turn may result in insulin resistance.

Keywords Adipocytes • Adipokines • Neonate growth • Neonate development • Metabolic syndrome • Birth weight

Introduction

Studies over the last several years have revealed important roles for adipose tissue that have been looked at with renewed interest. Adipose tissue is now regarded as a complex, highly active metabolic, endocrine organ. In fact, it secretes biologically active substances with systemic actions, such as leptin and adiponectin [1] and, besides playing a role in energy homeostasis, it contributes to immune and inflammatory responses.

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Both adipose tissue excess (i.e., obesity) and deficiency (i.e., lipodystrophy) are associated with adverse metabolic consequences, including insulin resistance, hyperglycemia, dyslipidemia, hypertension, prothrombotic and proinflammatory states.

Adipose tissue and its hormones are also involved in the growth and development of infants beginning early in neonatal life, with an influence on the risk of developing cardiovascular and cerebrovascular diseases in adulthood. In fact, pathogenetic mechanisms of these clinical conditions start very early in life. Epidemiological studies have demonstrated a link between reduced size at birth and/or rapid catch-up growth and increased long-term risk for adult onset obesity, insulin resistance, type 2 diabetes, hypertension and cardiovascular disease.

This chapter provides information on adipose tissue, its secreted molecules and their role in the physiological and pathological development of infants. A better understanding of adipose tissue biology and development may help to prevent and treat these clinical conditions.

Adipose Tissue

The traditional view of adipose tissue as a passive reservoir for energy storage is no longer valid. In fact, in 1987 it was discovered that it is one site for the metabolism of sex steroids and later, in 1994, that it secretes the hormone leptin. This latter finding clearly demonstrated a relationship between body fat and the endocrine axis, redefining adipose tissue as an endocrine organ.

Adipose tissue can accumulate in different compartments within the body, broadly defined as visceral (internal) and subcutaneous (peripheral). The accumulation of excess fat in the visceral compartment is associated with increased risk for multiple medical morbidities, including metabolic syndrome [2]. For example, type 2 diabetes and insulin resistance are linked to adipocyte hypertrophy in abdominal visceral adipose tissue (Fig. 25.1). The subcutaneous depots are less metabolically active, and secrete more leptin and adiponectin and less free fatty acids [2]. The excessive accumulation of subcutaneous adipose tissue is associated with hyperleptinemia which renders subjects more susceptible to further weight gain [3] (Fig. 25.1). This difference in disease risk may be due to differences in endocrine function among adipose tissue depots. Endocrine hormones derived from visceral adipose tissue are secreted into the portal system, have direct access to the liver and a relatively large effect on hepatic metabolic function. Therefore, it has been demonstrated that body fat distribution is critically important in patients with coronary heart disease rather than their total BMI [4] and that abdominal obesity is a stronger risk factor for mortality than general obesity [5]. Furthermore, subjects with fat around abdominal viscera in the mesentery and omentum (visceral fat) are at greater risk than those with peripheral obesity [6].

Adipose tissue is subdivided into two functionally distinct tissues, brown and white adipose tissue. Brown adipose tissue is specialized for heat production and the stored lipid droplets serve primarily as a fuel for the production of heat. White adipose tissue, on the other hand, represents a long-term energy reservoir storing triacylglycerols and protects other organs from mechanical damage [7]. An important feature of this tissue is that it is not made up simply of mature adipocytes which store lipids, but contains a variety of other cells such as fibroblasts, preadipocytes, tissue-resident macrophages and endothelial cells. Therefore, it expresses receptors sensitive to inflammatory agents and signals from the traditional hormone system as well as the central nervous system (CNS) (Table 25.1). These cells upon stimulation secrete large numbers of bioactive molecules, collectively termed adipokines, that act at both the local (autocrine/paracrine) and systemic (endocrine) level (Table 25.2). Adipokines (about 50 different molecular entities) include cytokines, growth factors, proteins of the alternative complement system and proteins involved in the regulation of blood pressure, vascular homeostasis, lipid metabolism, glucose homeostasis and angiogenesis. Adipose tissue is distributed in multiple subcutaneous, intra-abdominal, intramuscular and intrathoracic depots, which differ in receptor and adipokine expression and secretion, lipid storage capacity and fatty acid composition [1]. Adipose

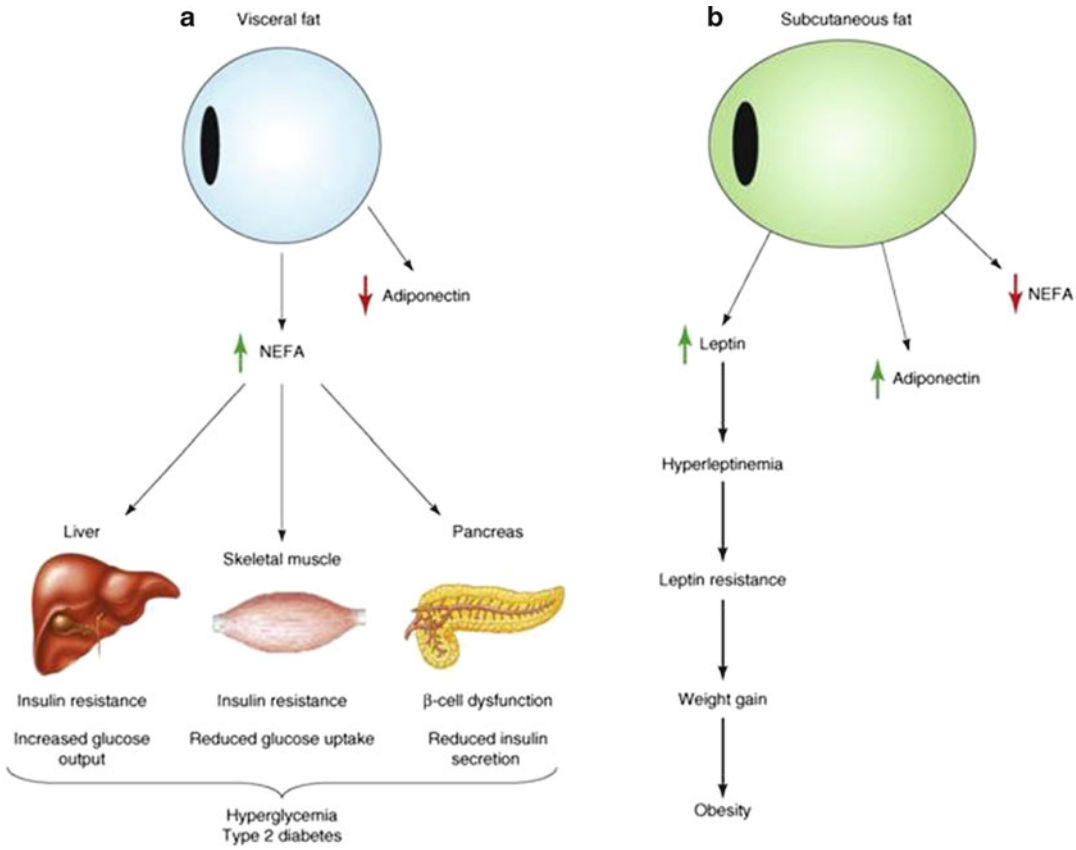

Fig. 25.1 Distinct roles of visceral (**a**) and subcutaneous (**b**) adipose tissue in whole-body metabolic functions (with the permission of the authors [57])

Table 25.1 Principal receptors expressed in adipose tissue

Receptors for endocrine hormones	Insulin receptor
	Glucagon receptor
	GH receptor
	TSH receptor
	Leptin receptor
	Angiotensin II receptors type 1 and 2
Nuclear hormone receptors	Glucocorticoid receptor
	Vitamin D receptor
	Thyroid hormone receptor
	Androgen, estrogen, and progesterone receptors
Cytokine receptors	IL-6 receptor
	TNF-α receptor
Catecholamine receptors	β1, β2, β3 receptors
	α1, α2 receptors

tissue is, therefore, involved in coordinating many biological processes including energy metabolism, neuroendocrine and immune function. In this latter process, adipose tissue-resident $CD4^+$ $CD31^+$ macrophages actively participate. Furthermore, the cross-talk between lymphocytes and adipocytes particularly in lymph nodes, which are generally surrounded by pericapsular adipose tissue [8], has an important role in regulating the immune system.

Table 25.2 Principal adipocyte-derived proteins with endocrine functions

Cytokines and chemokines	TNF-α
	IL-1, IL-6, IL-10, IL-15
	MCP-1, MIP
Hormones	Leptin
	Adiponectin
	Resistin
	Visfatin
	Nesfatin
Proteins involved in the fibrinolytic system	PAI-1
	Tissue factor
Lipids and proteins for lipid metabolism or transportation	Lipoprotein lipase (LPL)
	Cholesterol ester transfer protein (CETP)
	Apolipoprotein E
	Nonesterified fatty acids (NEFA)
Enzymes involved in steroid metabolism	Cytochrome P450-dependent aromatase
	17β-hydroxysteroid dehydrogenase (HSD)
	11βHSD1

Visceral adiposity is associated with chronic low-grade inflammation, as indicated by increased levels of the inflammatory markers CRP and IL-6 in the circulation of these obese subjects. On the other hand, severe malnutrition has been associated with thymic atrophy, reduced T-cell function and increased susceptibility to infection [9]. However, other factors such as poor hygienic conditions and concomitant chronic disease, which are also often present in severe malnutrition, might play an important role.

Adipose Tissue-Secreted Proteins

Adiponectin

Adiponectin is specifically expressed in differentiated adipocytes, principally in subcutaneous adipose tissue. This adipokine circulates at a high level (in the microgram per milliliter range) and it is a potent metabolic mediator that controls processes associated with obesity and inflammation. Serum adiponectin improves insulin sensitivity and fatty acid metabolism [10]; low levels are associated with obesity, type 2 diabetes, dyslipidemia, and cardiovascular/cerebrovascular diseases [11–14]. Serum adiponectin has strong anti-inflammatory properties in the vascular endothelium, pancreas, and intestinal mucosal epithelial cells.

Structurally, adiponectin belongs to the collagen superfamily, sharing homology with collagens, complement factors and also tumor necrosis factor (TNF)-α. Adiponectin occurs naturally as an oligomer based on the three-protein units whose peptide chains assemble as a collagen helix. The high molecular weight form is generally an 18mer, the intermediate weights include 6 and 12mers, the low molecular weight form is 3mers. The higher molecular weight complexes are the predominant form in human serum. Although total adiponectin concentrations play an important role in adult and childhood metabolic dysfunction, recent studies have highlighted the different activities of specific adiponectin oligomers. Different forms of adiponectin can display various, and sometimes opposing, activities. The ratio of these forms may be an important determinant of insulin sensitivity and response to insulin-sensitizing drugs [15, 16]. The 18mer high molecular weight form is highly active in controlling insulin-sensitive metabolic processes.

Adiponectin receptors were initially identified predominantly on muscle (AdipoR1) and liver cells (AdipoR2), although in humans they are expressed ubiquitously in the body.

Males have significantly lower plasma adiponectin levels than females, and this sexual dimorphism is observed during pubertal development in relation to serum androgens.

Clinical and animal studies consistently show decreased adiponectin levels in obesity, and these confer a substantially increased risk for diabetes and cardiovascular disease, suggesting that adiponectin may directly contribute to the pathogenesis of these diseases. Several lines of evidence support the protective role of adiponectin in the development of obesity-related disorders and metabolic syndrome, particularly in the pathogenesis of type 2 diabetes and cardiovascular/cerebrovascular diseases [17]. The metabolic effects of adiponectin are mediated by different mechanisms. For example, in the liver it increases fatty acid oxidation and reduces hepatic glucose output, via increased phosphorylation of the insulin receptor and modulation of the nuclear factor κB pathway [18].

Leptin

Leptin, a 16 kDa protein with a structure similar to cytokines, is encoded by the *Ob gene* [19] located on chromosome 7q31.3. It is principally secreted by subcutaneous adipose tissue. The leptin receptor (Ob-R) is a large single membrane-spanning protein and belongs to the gp130 family of cytokine class-I receptors.

Leptin affects central circuits in the hypothalamus, thereby suppressing food intake and stimulating energy expenditure. Thus, leptin plays a major role in the control of body fat stores through coordinated regulation of feeding behaviors, metabolism, autonomic nervous system, and body energy balance [20]. Congenital leptin deficiency is a rare cause of early-onset obesity. In all known cases, it has resulted in a dramatic reversal of the hyperphagia phenotype accompanied by hyperinsulinemia, hyperlipidemia and other metabolic, neuroendocrine and immune dysfunctions. Recombinant leptin therapy leads to a dramatic decrease in appetite and food intake, and to a complete reversal of hormonal changes such as hypogonadism seen in severely leptin-deficient subjects. DNA polymorphisms in the *Ob gene* may be linked to polygenic cases of obesity [20]. The level of *Ob mRNA* in white adipose tissue and the circulating leptin level are closely associated with the amount of fat mass, as shown in human and rodent studies. Leptin levels rapidly decline with caloric restriction and weight loss. In addition to its effects on energy homeostasis, leptin regulates neuroendocrine function and traditional endocrine systems. Leptin normalizes suppressed thyroid hormone levels in leptin-deficient humans via stimulation of TRH expression [21] and acts also on the ovaries, testes, prostate and placenta [22]. Other important endocrine effects of leptin include regulation of immune function, hematopoiesis, angiogenesis, and bone development. In fact, leptin normalizes immune function, promotes the proliferation and differentiation of hematopoietic cells, stimulates endothelial cell growth and angiogenesis [22]. Finally, leptin decreases bone mass via activation of the sympathetic nervous system [23].

Visfatin

It has been observed that the protein visfatin is increased in obesity. Visfatin has a molecular weight of 52 kDa. It was hypothesized to bind directly to the insulin receptor and to exert insulin-like effects both in vivo and in vitro [20, 24].

The effects of visfatin on adipogenesis and glucose metabolism are of particular interest with respect to its putative role in the pathogenesis of obesity and diabetes. Some clinical association studies have confirmed an association of visfatin with diabetes, while others did not find any correlation. Similarly, the relationship of visfatin with parameters of glucose metabolism and insulin resistance is contradictory, and overall there has been no clear effect demonstrated for visfatin on metabolism.

Resistin

Resistin received its name from the original observation that it induces insulin resistance in mice [25]. Resistin is an ~12 kDa polypeptide belonging to a unique family of cysteine-rich C-terminal domain proteins called resistin-like molecules. It is specifically expressed in adipose tissue, particularly in the visceral compartment (15-fold greater in rodents) [26].

Levels of resistin have been reported to be either increased, unchanged or decreased in obesity and type 2 diabetes, dampening the initial enthusiasm over the possible link between adiposity and insulin resistance. In fact, several studies in humans have failed to provide a clear and consistent link between resistin expression in adipose tissue or circulating resistin levels and adiposity or insulin resistance [26].

Interleukin (IL)-6 and TNF-α

IL-6 and TNF-α are the two best studied cytokines in obesity and have been consistently found to be increased in the serum of obese subjects [27]. Adipose tissue (adipocytes and adipose tissue matrix) contributes about 30 % of circulating IL-6, with visceral producing higher levels of IL-6 compared with subcutaneous adipose tissue [28]. IL-6 circulates in multiple glycosylated forms, ranging in size from 22 to 27 kDa. The IL-6 receptor (IL-6R) is homologous to the leptin receptor; a complex consisting of IL-6R and two homodimerized transmembrane gp130 molecules triggers intracellular signaling by IL-6.

IL-6 concentrations are positively correlated with obesity, impaired glucose tolerance, and insulin resistance [29]. They are high in obese subjects and decrease with weight loss. The high levels of IL-6 are probably responsible for the increase in acute-phase proteins, such as CRP. Furthermore, IL-6 induces hyperlipidemia and hyperglycemia, decreases insulin signaling and inhibits adipogenesis and adiponectin secretion [29]. These data suggest a causal role for IL-6 in obesity and insulin resistance.

Within adipose tissue, TNF-α is expressed by adipocytes, principally those of the subcutaneous tissue, and stromovascular cells [28]. TNF-α is a 26 kDa transmembrane domain protein that is cleaved into a 17 kDa biologically active protein, which exerts its effects via type I and type II TNF-α receptors. TNF-α is implicated in the pathogenesis of obesity and insulin resistance [30], by inducing serine phosphorylation of the insulin receptor, which inhibits insulin signaling [31]. Furthermore, it influences gene expression in metabolically important tissues, such as adipose tissue and liver. For example, TNF-α suppresses expression of genes involved in the uptake and storage of nonesterified fatty acids (adipose tissue) and in glucose uptake (liver) [32].

Adipose Tissue and Infant Development

A wide variation in the height and weight in the first years of life has been observed [33]. Most infants exhibit “catch-up” or “catch-down” growth over the first to second years of life [34] and these reflect the cessation of maternal-uterine influences on fetal growth. This growth also represents a move toward their genetic growth trajectory. The development of adipose tissue is very important in this period, since pathogenetic mechanisms of obesity start very early in life.

Humans differ from most mammals, including nonhuman primates, by accumulating significant quantities of body fat in the utero and consequently they have one of the highest fat ratios at birth. Until lactation is established, nutritional disruption is common at birth, during which time human newborns survive on fats deposited prenatally. This is one possible explanation for prenatal fat deposition.

The first traces of adipose tissue are already detectable between 14 and 16 weeks of gestation, both in males and females. Thus, in the second trimester there are early signs of adipogenesis and after the 23th week of prenatal life, the number of fat lobules remains constant and they only grow in size. At birth there is a large increase in heat production. It is known that a restriction in maternal nutrition reduces adipose tissue deposition. Therefore, infants born extremely preterm are profoundly deficient in adipose tissue and their postnatal course is often marked by prolonged nutritional compromise, chronic illness and poor growth [35]. This reduction refers only to subcutaneous and not to intraabdominal adipose tissue mass, suggesting that these two compartments may be under different regulatory control during intrauterine life [36]. This significantly increased intraabdominal adiposity may be due to excessive both endogenous (stress-associated glucocorticoid release) or exogenous (steroid treated subjects) glucocorticoid exposure. Evidence is presented that fat stores are mobilized during infection, hinting at one possible mechanism underlying the association between nutritional status and infectious morbidity and mortality among infants in nutritionally stressed human populations [37].

At birth, body fat accounts for ~16 % of body weight and during the first year of life the increase in body fat from about 0.7–2.8 kg is due to an increase in fat cell size rather than their number. Subcutaneous fat is greatest at about 9 months of life and, then, decreases until about 6 years, when it increases toward the pubertal spurt, at which time gender differences become apparent [38].

The mechanisms by which maternal and fetal/neonatal weights are regulated during human pregnancy and in early postnatal life are still poorly understood. Results of recent studies in newborns highlight the important issue that adipocytokines may play a crucial role in controlling fetal energy homeostasis and affecting deposition of adipose tissue in the utero. Epidemiological studies have shown an association between a reduced size at birth and increased long-term risk for obesity, insulin resistance, type 2 diabetes, hypertension and cardiovascular disease in adulthood [39, 40]. In particular, the transition from a relatively low birth weight to larger postnatal body size is associated with an increased risk for insulin resistance [41]. On the contrary, from a neurodevelopmental point of view, catch-up growth is important in small for gestational age (SGA) infants. Nutritional intervention in this case is justified. However, there is debate about the protective effect of breast milk versus childhood obesity [42]; it has been concluded that although a protective effect of breast milk remains plausible, the magnitude of the effect is quite small.

Despite several studies, it is difficult to trace the pathway by which events may lead to increased morbidity later in life. As discussed above, babies born with low birth weight have decreased fat accumulation in adipocytes and lack muscle mass, a deficiency that persists into childhood and adulthood. Therefore, it has been suggested that low birth weight may affect muscle structure and function and impair carbohydrate metabolism. The subsequent catch-up growth promotes excess adiposity in relation to muscle mass, which in turn may result in insulin resistance by the adipose tissue. Additionally, regulation of leptin and adiponectin production is altered in SGA during the catch-up growth period, childhood and adulthood, suggesting a role for these adipocytokines in determining insulin resistance [43–45]. Taken together, these observations support the concept of an alteration in adipose tissue during the period of fetal growth restriction extending to the postnatal period with long-term functional consequences in adults.

However, studies on the expression of adipocytokines during fetal and neonatal life and their relation to growth are sometimes contradictory. High leptin levels are observed in women during gestation, in cord blood at term and in capillary blood shortly after birth. It has been hypothesized that high leptin levels at term could represent an important feedback indicator of nutrient supply. Then, leptin levels decline rapidly and dramatically after birth in healthy neonates. This may be important for the stimulation of feeding behavior and the acquisition of energy homeostasis in the neonate [46]. Furthermore, leptin levels in cord blood are both closely related to adiposity in the newborn and strongly predictive of subsequent rates of weight gain [47].

Adiponectin, an insulin sensitizing hormone, changes inversely with acquisition of body fat. In fact, the leptin/adiponectin ratio correlates significantly with weight gain in mid-infancy, suggesting

that this ratio could be considered a marker related to infantile growth and later adiposity [48]. The adiponectin concentration in human cord blood is very high, which suggests a putative role in intrauterine fetal development, in particular a regulatory action on tissue differentiation, fetal growth and energy metabolism [49]. At birth adiponectinemia is still very high and this could reflect the newborn's body fat distribution, which is around 90 % in the subcutaneous compartment and only 4 % in the visceral, the inverse of that observed in the adult.

Furthermore, both leptin and adiponectin are present in breast milk suggesting that they may play a role in the early growth and development of breastfed infants [50].

Other authors have shown that both birth weight and the immediate postnatal growth velocity are not related to leptin or adiponectin levels, but only to the effects of an IGF-I spurt [51, 52]. In our previous study, we found no significant difference in adiponectin levels between appropriate for gestational age (AGA) and SGA infants at birth and during the first year of life, although SGA neonates weighed significantly less than AGA infants [53, 54]. These data were in accordance with other studies such as the one by Kamoda et al. [55]. In the same study, we found higher leptin levels in AGA neonates with respect to SGA infants at birth. On the contrary, at 1 year of age, SGA infants had leptin levels higher than AGA subjects, although the difference was not statistically significant. Since SGA infants show an increase in adipose tissue which is a typical phenomenon after a period of undernutrition, we speculated that the increased levels of leptin may derive from this increased adipose tissue and may be involved in the early development of insulin resistance.

Finally, it has also been shown that high resistin levels at term gestation could be advantageous to the infant by promoting hepatic glucose production and preventing hypoglycemia after birth [56].

Conclusions

We have described the role of adipose tissue and its secreted hormones in the development of neonates. Increased visceral adipose tissue mass in neonates seems to be a primary mechanism in early-life origins of obesity and metabolic disease after undernutrition or overnutrition during prenatal development. Adipose tissue-derived hormones such as leptin and adiponectin are deeply involved in the numerous functions of adipose tissue, from controlling energy homeostasis to interaction with the immune system. Recent evidence suggests a role for adipokines in the pathogenesis of metabolic syndrome, obesity and cardiovascular disease in childhood and adulthood.

A thorough understanding of the endocrine function of adipose tissue should enhance new approaches in the treatment of metabolic consequences due to excess or deficient adipose tissue.

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References

1. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab. 2004;89:2548–56.
2. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev. 2000;21:697–738.
3. Smith SR, Lovejoy JC, Greenway F, Ryan D, de Jonge L, de la Bretonne J, Volafova J, Bray GA. Contributions of total body fat, abdominal subcutaneous adipose tissue compartments, and visceral adipose tissue to the metabolic complications of obesity. Metabolism. 2001;50:425–35.
4. Coutinho T, Goel K, Corrêa de Sá D, Kragelund C, Kanaya AM, Zeller M, Park JS, Kober L, Torp-Pedersen C, Cottin Y, Lorgis L, Lee SH, Kim YJ, Thomas R, Roger VL, Somers VK, Lopez-Jimenez F. Central obesity and survival in subjects with coronary artery disease: a systematic review of the literature and collaborative analysis with individual subject data. J Am Coll Cardiol. 2011;57:1877–86.

5. Huffman DM, Barzilai N. Role of visceral adipose tissue in aging. Biochim Biophys Acta. 2009;1790:1117–23.
6. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Rev. 2009;11:11–8.
7. Trayhurn P. Adipocyte biology. Obes Rev. 2007;8:41–4.
8. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol. 2005;115:911–9.
9. Savino W. The thymus gland is a target in malnutrition. Eur J Clin Nutr. 2002;56:S46–9.
10. Berg AH, Combs TP, Scherer PE. ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. Trends Endocrinol Metab. 2002;13:84–9.
11. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T, Matsuzawa Y. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun. 1999;257:79–83.
12. Matsubara M, Maruoka S, Katayose S. Decreased plasma adiponectin concentrations in women with dyslipidemia. J Clin Endocrinol Metab. 2002;87:2764–9.
13. Matsuda M, Shimomura I, Sata M, Arita Y, Nishida M, Maeda N, Kumada M, Okamoto Y, Nagaretani H, Nishizawa H, Kishida K, Komuro R, Ouchi N, Kihara S, Nagai R, Funahashi T, Matsuzawa Y. Role of adiponectin in preventing vascular stenosis. The missing link of adipo-vascular axis. J Biol Chem. 2002;277:37487–91.
14. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab. 2001;86:1930–5.
15. Fisher FF, Trujillo ME, Hanif W, Barnett AH, McTernan PG, Scherer PE, Kumar S. Serum high molecular weight complex of adiponectin correlates better with glucose tolerance than total serum adiponectin in Indo-Asian males. Diabetologia. 2005;48:1084–7.
16. Pajvani UB, Hawkins M, Combs TP, Rajala MW, Doebber T, Berger JP, Wagner JA, Wu M, Knopps A, Xiang AH, Utzschneider KM, Kahn SE, Olefsky JM, Buchanan TA, Scherer PE. Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. J Biol Chem. 2004;279:12152–62.
17. Kiess W, Petzold S, Töpfer M, Garten A, Blüher S, Kapellen T, Körner A, Kratzsch J. Adipocytes and adipose tissue. Best Pract Res Clin Endocrinol Metab. 2008;22:135–53.
18. Díez JJ, Iglesias P. The role of the novel adipocyte-derived hormone adiponectin in human disease. Eur J Endocrinol. 2003;148:293–300.
19. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994;372:425–32.
20. Korner A, Kratzsch J, Kiess W. Adipocytokines: leptin–the classical reistin–the controversial, adiponectin–the promising and more to come. Best Pract Res Clin Endocrinol Metab. 2005;19:525–46.
21. Bjørbaek C, Kahn BB. Leptin signaling in the central nervous system and the periphery. Recent Prog Horm Res. 2004;59:305–31.
22. Margetic S, Gazzola C, Pegg GG, Hill RA. Leptin: a review of its peripheral actions and interactions. Int J Obes Relat Metab Disord. 2002;26:1407–33.
23. Cock TA, Auwerx J. Leptin: cutting the fat off the bone. Lancet. 2003;362:1572–4.
24. Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, Matsuki Y, Murakami M, Ichisaka T, Murakami H, Watanabe E, Takagi T, Akiyoshi M, Ohtsubo T, Kihara S, Yamashita S, Makishima M, Funahashi T, Yamanaka S, Hiramatsu R, Matsuzawa Y, Shimomura I. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science. 2005;307:426–30.
25. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA. The hormone resistin links obesity to diabetes. Nature. 2001;409:307–12.
26. Banerjee RR, Lazar MA. Resistin: molecular history and prognosis. J Mol Med (Berl). 2003;81:218–26.
27. Cottam DR, Mattar SG, Barinas-Mitchell E, Eid G, Kuller L, Kelley DE, Schauer PR. The chronic inflammatory hypothesis for the morbidity associated with morbid obesity: implications and effects of weight loss. Obes Surg. 2004;14:589–600.
28. Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. Endocrinology. 2004;145:2273–82.
29. Fernández-Real JM, Ricart W. Insulin resistance and chronic cardiovascular inflammatory syndrome. Endocr Rev. 2003;24:278–301.
30. Ruan H, Lodish HF. Insulin resistance in adipose tissue: direct and indirect effects of tumor necrosis factor-alpha. Cytokine Growth Factor Rev. 2003;14:447–55.
31. Hotamisligil GS, Murray DL, Choy LN, Spiegelman BM. Tumor necrosis factor alpha inhibits signaling from the insulin receptor. Proc Natl Acad Sci U S A. 1994;91:4854–8.

32. Ruan H, Miles PD, Ladd CM, Ross K, Golub TR, Olefsky JM, Lodish HF. Profiling gene transcription in vivo reveals adipose tissue as an immediate target of tumor necrosis factor-alpha: implications for insulin resistance. Diabetes. 2002;51:3176–88.
33. Tanner JM. Growth from birth to two: a critical review. Acta Medica Auxologica. 1994;26:7–45.
34. Smith DW, Truog W, Rogers JE, Greitzer LJ, Skinner AL, McCann JJ, Harvey MA. Shifting linear growth during infancy: illustration of genetic factors in growth from fetal life through infancy. J Pediatr. 1976;89:225–30.
35. Uthaya S, Thomas EL, Hamilton G, Doré CJ, Bell J, Modi N. Altered adiposity after extremely preterm birth. Pediatr Res. 2005;57:211–5.
36. Harrington TA, Thomas EL, Frost G, Modi N, Bell JD. Distribution of adipose tissue in the newborn. Pediatr Res. 2004;55:437–41.
37. Kuzawa CW. Adipose tissue in human infancy and childhood: an evolutionary perspective. Am J Phys Anthropol. 1998;107 Suppl 27:177–209.
38. Boulton TJ, Dunlop M, Court JM. The growth and development of fat cells in infancy. Pediatr Res. 1978;12:908–11.
39. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ. 1989;298:564–7.
40. Eriksson JG, Forsen T, Tuomilehto J, Jaddoe VWV, Osmond C, Barker DJP. Effects of size at birth and childhood growth on the insulin resistance syndrome in elderly individuals. Diabetologia. 2002;45:342–8.
41. Dunger DB, Ong KK. Babies born small for gestational age: insulin sensitivity and growth hormone treatment. Horm Res. 2005;64:58–65.
42. Ong KK, Preece MA, Emmett PM, Ahmed ML, Dunger DB. ALSPAC Study Team. Size at birth and early childhood growth in relation to maternal smoking, parity and infant breast-feeding: longitudinal birth cohort study and analysis. Pediatr Res. 2002;52:863–7.
43. Jaquet D, Gaboriau A, Czernichow P, Levy-Marchal C. Relatively low serum leptin levels in adults born with intrauterine growth retardation. Int J Obes Relat Metab Disord. 2001;25:491–5.
44. Jaquet D, Deghmoun S, Chevenne D, Czernichow P, Lévy-Marchal C. Low serum adiponectin levels in subjects born small for gestational age: impact on insulin sensitivity. Int J Obes (Lond). 2006;30:83–7.
45. Cianfarani S, Martinez C, Maiorana A, Scirè G, Spadoni GL, Boemi S. Adiponectin levels are reduced in children born small for gestational age and are inversely related to postnatal catch-up growth. J Clin Endocrinol Metab. 2004;89:1346–51.
46. Schubring C, Siebler T, Kratzsch J, Englaro P, Blum WF, Triep K, Kiess W. Leptin serum concentrations in healthy neonates within the first week of life: relation to insulin and GH levels, skin fold thickness, BMI and weight. Clin Endocrinol. 1999;51:199–204.
47. Ong KK, Ahmed ML, Dunger DB. The role of leptin in human growth and puberty. Acta Paediatr Suppl. 1999;88:95–8.
48. Diamon F, Dharamraj C, Luther S, Eichler D. The leptin/adiponectin ratio in mid-infancy correlates with weight gain in healthy term infants, but is unrelated to serum insulin concentrations, body mass index, or skin fold thickness. J Pediatr Endocrinol Metab. 2008;21:1133–8.
49. Cortelazzi D, Corbetta S, Ronzoni S, Pelle F, Marconi A, Cozzi V, Cetin I, Cortelazzi R, Beck-Peccoz P, Spada A. Maternal and foetal resistin and adiponectin concentrations in normal and complicated pregnancies. Clin Endocrinol (Oxf). 2007;66:447–53.
50. Woo JG, Guerrero ML, Altaye M, Ruiz-Palacios GM, Martin LJ, Dubert-Ferrandon A, Newburg DS, Morrow AL. Human milk adiponectin is associated with infant growth in two independent cohorts. Breastfeed Med. 2009;4:101–9.
51. Petridou E, Skalkidou A, Dessypris N, Kedikoglou S, Mantzoros C, Chroussos G, Trichopoulos D. Growth velocity during the first postnatal week of life is not related to adiponectin or leptin. Paediatr Perinat Epidemiol. 2004;18:395.
52. Lindsay RS, Walker JD, Havel PJ, Hamilton BA, Calder AA, Johnstone FD. Adiponectin is present in cord blood but is unrelated to birth weight. Diabetes Care. 2003;26:2244–9.
53. Strocchio L, Bozzola E, Cerbo RM, Meazza C, Travaglino P, Pagani S, Laarej K, Stronati M, Bozzola M. Changes in circulating levels of adiponectin and leptin in children during the first two years of life. Minerva Pediatr. 2007;59:739–44.
54. Bozzola E, Meazza C, Arvigo M, Travaglino P, Pagani S, Stronati M, Gasparoni A, Bianco C, Bozzola M. Role of adiponectin and leptin on body development in infants during the first year of life. Ital J Pediatr. 2010;36:26.
55. Kamoda T, Saitoh H, Saito M, Sugiura M, Matsui A. Serum adiponectin concentrations in newborn infants in early postnatal life. Pediatr Res. 2004;56:690–3.
56. Ng PC, Lee CH, Lam CW, Chan IH, Wong E, Fok TF. Resistin in preterm and term newborns: relation to anthropometry, leptin, and insulin. Pediatr Res. 2005;58:725–30.
57. Muhlhausler B, Smith SR. Early-life origins of metabolic dysfunction: role of the adipocyte. Trends Endocrinol Metab. 2009;20:51–7.

Chapter 26
Role of Fatty Acids in the Neurological Development of Infants

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Key points

- There is plausible evidence from both well-designed epidemiological and maternal supplementation studies (during pregnancy and/or lactation) that support an important role for long-chain polyunsaturated fatty acids (LCPUFAs), particularly docosahexaenoic acid (DHA), in the neurodevelopment of infants and children.
- The benefits of DHA supplementation during pregnancy and lactation may persist till 7 years of age.
- Recent consensus statements by expert panels including the Perinatal Lipid Metabolism Organization (PeriLip), the Early Nutritional Programming Group (EARNEST), the European Food Safety Authority, and the Food and Agricultural Organization of the United Nations have recommended that pregnant and lactating women should aim to achieve an average dietary intake of at least 200 mg DHA/day.
- Supplementation with LCPUFAs for more than 6 months increases the likelihood of observing beneficial effects on cognitive function in infants.
- A DHA concentration of 0.32 % of total fatty acids during the first year of life appears adequate to improve cognitive function during infancy.
- The majority of studies of preterm and term infants have demonstrated that arachidonic acid (ARA) in a DHA-supplemented infant formula is critical for optimal growth. Up to 0.64 % of ARA of total fatty acids is generally recognized as safe and is routinely included in commercially available infant formulas in the United States and elsewhere.

Keywords Long-chain polyunsaturated fatty acids • Docosahexaenoic acid • Arachidonic acid • Infant neurodevelopment • Nutritional supplementation • Clinical trials

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Introduction

The long-chain polyunsaturated fatty acids (LCPUFAs), docosahexaenoic acid (DHA, 22:6n-3) and arachidonic acid (ARA, 20:4n-6), are essential structural components of the central nervous system [1–4]. DHA is of particular importance because it is specifically concentrated in the structural membrane lipids of the white and gray matter of the brain and the visual elements of the retina [1, 4]. The human brain undergoes rapid growth during the first 2 years of life [5] during which there is a large concomitant accumulation of DHA [2]. Based on autopsy information, from the third trimester to about 2 years of age, there is a 12-fold increase in brain size. The increase in brain size is accompanied by an approximate fourfold increase in DHA and ARA concentrations in tissue [6].

The amount of DHA in the brain is continually turned over, recycled, and replenished by uptake from plasma [7]. Estimates by Hadley et al. [8] suggest that the amount of DHA accumulated daily in the brain of infants is ~1.45 mg while the daily turnover rate is ~3.75 mg of DHA. The dietary requirement to compensate for the accretion and turnover is estimated to be 5.2 mg/day of DHA (1.45+3.75 mg/day) [8]. DHA is available from either preformed DHA or from the conversion of DHA from α-linolenic acid (ALA). However, the conversion of ALA to DHA is very limited (< 1 %) [9–11]. To maintain homeostasis of DHA (5.2 mg/day) in the brain, over 200 mg/day of dietary DHA is needed, assuming that only 1.7 % of preformed dietary DHA reaches the brain [12] and the remainder is provided from the conversion of ALA to DHA [8]. Furthermore, the earlier an infant is born preterm, the lower the levels of DHA and ARA, putting optimal neurodevelopment at risk.

Neither DHA nor ARA can be formed de novo by mammalian cells [7]. Therefore, the infant needs an exogenous source or the adequate precursors ALA and linoleic acid (LA, 18:2n-6), respectively, in the diet. The most available source of DHA is fish, especially fatty fish, although food enriched with fish oil or algal-DHA are also excellent sources. DHA and ARA are naturally found in human milk and are now included in almost all commercially available infant formulas. For the fetus, these fatty acids are derived from the mother by placental transfer and after birth by the infant diet (human milk or formula). There is a specific transport mechanism for the placental transfer of DHA from the mother to the fetus [13]. The levels of DHA in human milk are greatly influenced by the amount of DHA provided in the diet [7]. The amount of DHA in human milk is increased by increasing maternal intake [14]. Human milk concentrations of DHA vary widely and range from 0.17 to 0.99 wt.%, with the highest levels in Japanese milk and the lowest levels in Canadian and US samples [15]. However, only modest variations in ARA levels in human milk are observed (0.36–0.49 wt.%) across different populations [15].

Supplementation with ALA during pregnancy does not increase DHA in maternal or infant blood lipids [16]. Similarly, during lactation, ALA supplementation has no measurable effect on the amount of DHA present in human milk [14]. Adding increasing amounts of ALA in infant formula also do not significantly raise the blood levels of DHA in formula-fed infants [17]. Thus, for both the preterm and term infants, preformed DHA is essential.

LA is the shorter chain precursor of ARA. By sharing the same enzymatic pathways as for the elongation and desaturation of ALA to eicosapentaenoic acid (EPA, 20:5n-3) and DHA, the n-6 fatty acid LA is converted into the LCPUFA ARA. As in the n-3 conversion, the n-6 conversion is inefficient. The relationship of n-6 and n-3 fatty acids is important both for the precursors and end products [18]. Most infant formula guidelines require the ratio of LA:ALA not to be less than 5 or greater than 15. In addition, when preformed DHA is added to infant formula, ARA must also be added at an amount which is equal to, or greater than, the level of DHA [19].

Recent studies have shown that DHA status is influenced not only by diet, but also by genetic variants, single nucleotide polymorphisms (SNPs) in the fatty acid desaturases (*FADS*) [20, 21]. *FADS* and red blood cell fatty acid data from the Avon Longitudinal Study of Parents and Children indicate that, independent of dietary effects, polymorphisms in the desaturase encoding genes *FADS1* and *FADS2* were positively associated with the precursor fatty acids LA and ALA and negatively associated with

DHA and ARA [21]. Similar but weaker associations were shown for the *FADS3* gene [21]. These data confirm previously reported findings from smaller studies that suggest a decline in desaturase expression for the production of DHA and ARA [22, 23]. However, the genetically explained variability of red blood cell DHA and ARA levels were very low (0.51 % and 1.13 %, respectively) [21]. Further, the effect of *FADS* genetic variants on LCPUFA metabolism, specifically ARA, appears to vary at the population level. Compared with European Americans, African Americans have significantly higher circulating levels of plasma ARA and lower levels of dihomo-gamma-linolenic acid. A larger proportion of African Americans carry the genotype associated with increased *FADS1* enzymatic conversion of dihomo-gamma-linolenic to ARA [24]. The extent to which levels of DHA, ARA, and other fatty acids are affected by FADS genotypes needs further study.

In a recent meta-analysis of four clinical trials including data for preterm and term infants, LCPUFA supplementation had no effect on Bayley Developmental scores at 18 months of age. [25] However, in a systematic review of over 20 randomized clinical trials (RCTs) involving term infants who received DHA and ARA supplemented formula or a control formula, Hoffman and his colleagues [26] noted that differing levels of DHA greatly influenced outcomes related to cognition and visual acuity. Clinical trials that considered infant formulas containing levels of DHA close to the worldwide human milk mean of 0.32 % of total fatty acids were more likely to yield positive results [26]. There was also some evidence to suggest that an ARA:DHA ratio greater than 1:1 was associated with improved cognitive outcomes [26]. In a meta-analysis of preterm infants fed a DHA-containing formula vs. a DHA-free formula, those fed DHA had significantly better visual acuity at 2 and 4 months of age [27]. Meta-analyses are sometimes difficult to interpret because they typically cannot correct for different outcomes, doses, length of exposure, or different patient populations. As a result, important outcomes from individual studies are obscured.

Since the publication of the review by Hoffman et al. [26], several epidemiological and intervention studies have appeared in the literature. Additional research has focused on the effects that LCPUFA supplementation during pregnancy and lactation has on neurodevelopment and visual function of infants and children. The long-term effects of LCPUFA supplementation during infancy on several health outcomes have also been recently published. In this chapter, we evaluate the recent evidence of the role that fatty acids, specifically DHA and ARA, play in the neurological development (visual, cognitive, motor function) of preterm and term infants.

Epidemiological Studies of LCPUFA Intake During Pregnancy and Infancy

The epidemiological studies of LCPUFA intake during pregnancy and infancy are listed in Table 26.1. Bakker et al. [28] considered the relationship between motor function (Maastricht Motor Test, MMT) at age 7 ($n = 306$) and LCPUFA levels (DHA and ARA) in umbilical venous plasma phospholipids at birth and in plasma phospholipids at 7 years of age. There was a significant, positive relationship between umbilical plasma DHA levels and the MMT score (both total and quality score) at 7 years of age. The investigators concluded that prenatal DHA availability, which is influenced by maternal diet during pregnancy, can have a positive effect on the quality of motor function later in life.

Using data from a food frequency questionnaire administered shortly after delivery, the relationship between seafood intake during pregnancy and child neurodevelopment (McCarthy Scales of Children's Abilities, MCSA) at 4 years of age was evaluated [29]. Shellfish and squid were analyzed separately from fish because these types of seafood typically have lower levels of DHA [30]. Among children ($n = 392$) who were breastfed for <6 months, maternal fish intake of >2–3 times/week was associated with significantly higher scores on several MCSA subscales at 4 years of age compared with maternal fish intakes of ≤1 time/week. There was no association observed among children who were breastfed for a longer period (≥ 6 months). Maternal intakes of shellfish and squid were inversely related to several MCSA subscales regardless of the breastfeeding duration. The lack of an association among

Table 26.1 Epidemiological studies of LCPUFA supplementation

Author (Year)	Location	*N* (enrolled)	Supplementation		Functional measurements: age at assessment	Effects of supplementation	
			Duration	Dose		Functional	Biochemical DHA status
Bakker et al. [28]	The Netherlands	306 children	4.6 ± 4.6 months	I: Breast fed C: Formula w/out LCPUFA	MMT: 7 years	↑ scores in I vs. C (NS)	↑ in children in I
Mendez et al. [29]	Spain	482 women 392 children for follow-up	N/A	*Seafood intake* G1: ≤1.5 times/week G2: ≥1.5 to times/week G3: > 2–3 times/ week G4: > 3 times/week	MCSA: 4 years	↑ scores in G3 vs. G1 when breast fed <6 months ($p < 0.05$)	N/A
Tanaka et al. [31]	Japan	38 infants	At least 6 months	I: Breast fed C: Formula fed	KABC, D-N test, KRISP, MPT, SDQ: 5 years	↑ sequential processing scores in KABC in I vs. C ($p < 0.05$) ↑ D-N test, KRISP and MPT scores in I vs. C ($p < 0.05$) ↑ hyperactive and emotional scores in SDQ in C vs. I ($p < 0.05$)	↑ DHA at 4 weeks of age in I vs. C ($p < 0.05$)
Gale et al. [32]	UK	241 children	6 months	I1: Fortified formula I2: Breast milk C: Unfortified formula	WPPSI III, NEPSY, TVPS: 4 years	↑ IQ scores in WPPSI III in I2 vs. C ($p < 0.05$)	N/A
Keim et al. [33]	USA	408 maternal-infant pairs	4 months	G1: Exclusively breast fed G2: Almost exclusively breast fed G3: Exclusively formula fed G4: Partially breast fed	MDA: 12 months	↑ scores in G1 vs. G3 (NS)	N/A
Rioux et al. [36]	Canada	96 pregnant women 63 maternal-infant pairs for testing	N/A	*Gestational iron status* G1: Anemic G2: Low iron stores G3: Iron deficiency anemia	BL, BSID: 6 months ± 4 weeks	None	None

BL Brunet-Lezine Scale of Psychomotor Development of Early Childhood; *BSID* Bayley Scales of Infant Development; *C* control; *DHA* docosahexaenoic acid; *D-N test* Day-Night test; *G*, group; *I* intervention; *KABC* Kaufman Assessment Battery for Children; *KRISP* Kansas Reflection Impulsivity Scale for Preschoolers; *LCPUFA* long-chain polyunsaturated fatty acids; *MCSA* McCarthy Scales of Children's Abilities; *MDA* Mullen developmental assessment; *MMT* Maastricht Motor Test; *MPT* Motor Planning Teat; *N/A*, not applicable; *NEPSY* Developmental Neuropsychological Assessment; *NS* not significant; *SDQ* Strengths and Difficulties Questionnaire; *TVPS* Test of Visual-Perceptual Skills; *WPPSI III* Wechsler Pre-School and Primary Scale of Intelligence; $p < 0.05$ = significant

children breastfed for ≥6 months was attributed to a ceiling effect because DHA in human milk was provided for a longer period of time. The negative associations observed with shellfish and squid were probably related to the effects of methyl mercury contamination reported in these types of seafood.

In a small follow-up study conducted in Japan, 18 of 38 very-low-birth-weight infants (<1,200 g) who were enrolled were classified into groups that were breastfed ($n=10$) or formula-fed (with or without human milk, $n=8$) [31]. The duration of breastfeeding in the breastfed group was 72 ± 45 days whereas the duration of breastfeeding in the formula group was 59 ± 32 days. DHA concentration in the red blood cells was measured at 4 weeks of age. Cognitive function at the age of 5 years was evaluated using five tests: the Kaufman Assessment Battery for Children, Day-Night Test, Kansas Reflection Impulsivity Scale for Preschoolers (KRISP), Motor Planning Test, and Strengths and Difficulties Questionnaire. The concentration of DHA in red blood cells was significantly higher in the breastfed infants compared with the formula-fed infants (4.1 % vs. 2.7 %, respectively). The scores for the Day-Night Test, KRISP, and Motor Planning Test were significantly higher in the breastfed group. There were also significant correlations between the levels of DHA concentration at 4 weeks of age and scores on the Day-Night Test and KRISP tests. Despite the small sample size, the authors concluded that DHA supplied by breastfeeding in early infancy among very-low-birth-infants had a positive effect on their neurodevelopment, especially aspects of executive function at 5 years of age.

Infant feeding data from the Southampton Women's Survey were used to investigate the relationship between breastfeeding, LCPUFA-fortified formula and unfortified formula feeding, and neuropsychological function in 4-year-old children ($n=241$) [32]. A milk feeding history was obtained at birth and at 6 months of age. There were 130 children in the breastfed group (54%), 65 in the fortified-formula group (27 %), and 46 in the unfortified-formula group (19 %). At 6 months of age, the estimated DHA intake in the three groups was 12.1, 13.0, and 2.1 g, respectively. After adjusting for several demographic characteristics (maternal age, parity, education, occupational social class), at 4 years of age, there were no differences in IQ scores between the breastfed and fortified-formula groups, but there was a significant difference in IQ scores between the fortified-formula and unfortified-formula groups. However, there was no evidence for any correlations associated with the estimated intake of DHA and IQ scores. This finding may reflect inaccuracies in the estimation of DHA intake or that the IQ advantage was related to confounding factors that were not measured (e.g., home environment).

Data from an observational study of infant feeding practices from the Pregnancy, Infection, and Nutrition Study ($n=358$) were used to examine LCPUFA concentration of human milk and infant formulas fed during the first 4 months of life in relation to cognitive development at 12 months of age (Mullen Developmental Assessment) [33]. The results indicated that exclusive breastfeeding and DHA content of human milk or infant formula were not associated with improved infant development. These findings were not unexpected considering the weaknesses of the study design. Firstly, there was no control group. Only a few infants ($n=3$) were fed formulas without DHA and ARA for all 4 months. Secondly, the sample size of the reference group (exclusively formula fed) used for comparison (vs. exclusively or almost exclusively breastfed and partially breastfed infants) was small ($n=39$) and statistically underpowered. Thirdly, the ranges of DHA and ARA concentrations in human milk and infant formula were wide compared to those used in most previously published infant formula trials [33] and the levels overlapped between the feeding groups. The reported levels of DHA and ARA in human milk ranged from 0.07 % to 1.49 % and 0.05–1.52 % of total fatty acids, respectively. The LCPUFA concentration of formulas ranged from 0.30 % to 0.37 % for DHA and from 0.50 % to 0.67 % for ARA. Fourthly, an assessment of the concentration of DHA and ARA in table foods provided to infants from 4 months to 12 months of age was not conducted. Finally, the Mullen Developmental Assessment may not be the best test to detect subtle mental and motor developmental benefits related to LCPUFA [33]. Previous studies that have reported positive associations between LCPUFAs and infant neurodevelopment have typically used the Bayley Scales of Infant Development [26].

In an analysis of eight RCTs, conducted prior to 2005, that compared children who received LCPUFA supplemented infant formula (7 studies) or maternal dietary supplementation (1 study) vs.

controls, Cohen et al. [34] estimated that every 100 mg/day of DHA increased the child's IQ by 0.13 points. While the increase in IQ seems small, at the population level, the impact on public health could be significant.

Fish consumption, considered a surrogate for omega-3 fatty acid consumption, was associated with cognitive outcomes (Denver Developmental Screening Test, Strengths and Difficulties Questionnaire, IQ) in the Avon Longitudinal Study of Parents and Children Study (ALSPAC) of 11,875 pregnant women [35]. Children from mothers with no seafood consumption were at greatest risk of adverse or suboptimal outcomes. Greater maternal intake of omega-3 fatty acids was associated with a lower risk of sub-optimal verbal IQ. Overall, consumption of more than 340 g seafood per week was beneficial for the child's neurodevelopment.

The relationship between maternal DHA and iron status at 28–32 weeks of gestation and infant cognitive performance (Brunet-Lézine Scale of Psychomotor Development of Early Childhood and the Bayley Scales of Infant Development) at 6 months of age was evaluated in a small group of Canadian infants ($n=63$) born to mothers with a privileged socioeconomic background [36]. A significant association between pregnant women's iron and DHA status and their infant's cognitive performance was not observed. The majority of infants was exclusively breastfed at birth (81 %), and slightly less than half (41 %) were exclusively breastfed at 4 months of age. Among infants, the majority was fed an iron-fortified formula and nearly 50 % were fed a formula containing LCPUFAs [36]. Only a small percentage of pregnant women had iron-deficiency anemia (3.2 %) or anemia (9.5 %) and the mean levels of DHA in plasma and erythrocytes were adequate (2.13 ± 0.5 and 4.31 ± 1.98, respectively). The lack of significant association between pregnant women's iron and DHA status and their infant's cognitive performance was probably related to the fact that most infants received adequate amounts of DHA by placental transfer or from their diet. Identifying subtle differences in cognitive development is challenging in well-designed clinical trials with large sample sizes [37]. In studies with small samples sizes, particularly those that consider infants from a privileged socioeconomic background, a ceiling effect of neurocognitive development may be reached in which the majority of infants have achieved their genetic potential for optimal cognitive development. Well-designed and properly statistically powered studies among underprivileged infants would increase the likelihood of detecting significant relationships between LCPUFA supplementation and infant neurodevelopment.

Studies of LCPUFA Supplementation During Pregnancy and/or Lactation and Neurodevelopment in Children

A systematic review of 13 RCTs considered the effects that LCPUFA supplementation during pregnancy and/or lactation had on neurodevelopment and visual function of children [38]. All studies in the review were published prior to 2008 and are not considered in the present chapter. Dziechciarz et al. [38] reported that many of the studies had important methodological limitations such as the failure to indicate whether the study was blinded or whether incomplete outcome data were adequately addressed. According to the authors, evidence from the 13 studies did not demonstrate a clear and consistent benefit of n-3 LCPUFA supplementation during pregnancy and/or lactation on child neurodevelopment and visual acuity. However, with respect to supplementation during pregnancy, one study showed significantly better eye and hand coordination at 30 months of age [39] and another demonstrated a n-3 LCPUFA benefit on problem solving [40]. Considering supplementation during lactation, one study showed significant improvement on the Bayley Psychomotor Development Index at 30 months of age [41].

We consider one study that evaluated maternal LCPUFA supplementation during pregnancy and/or lactation and neurocognitive development of infants at 18 months of age [42] (Table 26.2).

Table 26.2 Maternal LCPUFA supplementation studies and follow-up studies of children to 7 years of age

Author (Year)	Location	*N* (enrolled)	Supplementation		Functional measurements: age at assessment	Effects of supplementation	
			Duration	Dose		Functional	Biochemical DHA status
Maternal LCPUFA supplementation studies							
Makrides et al. [42]	Australia	726 children	Study entry until birth	I:Fish oil (800 mg/d of DHA + 100 mg/d of EPA)	BSID III: 18 months	None	N/A
		2,399 women		C: Vegetable oil capsules w/out DHA			
Maternal LCPUFA supplementation follow-up studies							
Smithers et al. [45]	USA	143 preterm infants	From enrollment until term	I: 1% DHA C: .2–0.3% DHA	MCDI: 26 months SDQ, STSC: between 3 and 5 years	None	N/A
Escolano-Margarit et al. [46]	Germany, Spain, Hungary	315 pregnant women	From week 20 of pregnancy until delivery	*Women*	HE: 4 years	None	↑ in infants at 30 weeks of gestation and at delivery in G1 vs. G2
		270 infants for follow-up		I1: Fish oil (500 mg DHA + 150 mg EPA) I2: 400 μg 5-MTHF I3: I1 + I2 C: Placebo *Infants* G1: I1 + I3 infants fed formula with 0.5 % DHA + 0.4 % ARA G2: I2+C infants fed formula w/out DHA + ARA	TE: 5.5 years		None found at 4 and 5.5 years
Jensen et al. [47]	USA	230 infants	Delivery until 4 months postpartum	I: DHA algal oil (200 mg/day of DHA) C: Vegetable oil (no DHA)	Bayley PDI: 30 months MSCA, KABC, PPT, WPPSI-R, LIPS-R: 5 years	↑ sustained attention scores in LIPS-R in I vs. C ($p<0.05$)	N/A
Cheatham et al. [48]	Denmark	122 women 98 children for follow-up	First 4 months of lactation	I: Fish oil (0.79 g DHA +0.62 g EPA) C: Olive oil RG: High–fish intake (0.82 g/day of n-3 LCPUFA)	WJTCA III, D/N Stroop task, SDQ: 7 years	None	↑ in children in I and RG

5-MTHF 5-methyltetrahydrofolate; *ARA* arachidonic acid; *BSID* Bayley Scales of Development; *C* control; *DHA* docosahexaenoic acid; *D/N Stroop task* Day/Night Stroop task; *EPA* eicosapentaenoic acid; *G* group; *HE* Hempel examination; *I* intervention; *KABC* Kaufman Assessment Battery for Children; *LCPUFA* long-chain polyunsaturated fatty acids; *LIPS-R* Leiter International Performance Scale-Revised; *MCDI* MacArthur Communicative Development Inventory; *MSCA* McCarthy Scales of Children's Abilities; *N/A* not applicable; *NS* not significant; *PDI* Psychomotor Development Index; *PPT* Purdue Pegboard Test; *RG* reference group; *SDQ* Strengths and Difficulties Questionnaire; *STSC* Short Temperament Scale for Children; *TE* Touwen examination; *WJTCA III* Woodcock Johnson Tests of Cognitive Abilities III; *WPPSI-R* Wechsler Primary and Preschool Scale of Intelligence-Revised; $p<0.05$ = significant

Four studies involving LCPUFA supplementation during pregnancy and/or lactation were follow-up studies. These studies followed a cohort of children up to 3–7 years since the initial LCPUFA supplementation (Table 26.2).

A double-blind, multicenter, randomized control trial (DHA to Optimize Mother Infant Outcome, DOMinO) considered 2,399 women from five Australian maternity hospitals who were provided 800 mg/day of DHA and 100 mg/day of EPA starting at 21 weeks of gestation until delivery [42]. The main objective of the study was to determine whether DHA supplementation during pregnancy decreased symptoms of postpartum depression. In addition, 694 children were evaluated at 18 months using the Bayley Scales of Infant and Toddler Development (BSID-III). Compared to placebo, while the trend was favorable toward the DHA group, supplementation with DHA did not significantly lower the levels of postpartum depression. Further, mean cognitive and mean language composite scores did not differ between treatment groups, but fewer children in the DHA group had delayed cognitive development compared with those in the control group. However, girls in the DHA treatment group had lower language scores and were more likely to show delayed language development than those in the control group. Notably, there were fewer very preterm births (<34 weeks of gestation) in the DHA group compared with the control group. Women in the DHA group also had heavier infants and fewer infant admissions to the neonatal intensive care unit. Unfortunately, the authors did not report food intake of infants after birth making it difficult to determine the amount of DHA provided from human milk or infant formula. As a result, any potential differences in cognitive performance between groups due to the initial study treatment may have diminished over time. In an accompanying editorial, Oken and Belfort [43] noted that improved DHA status may reduce the risk for preterm birth and may have benefits not reported in the study. Pregnant women should continue to include DHA in their diet and receive the recommended intake of 200 mg of DHA/day [43].

In a follow-up study of infants who were enrolled in the DHA for the Improvement in Neurodevelopmental Outcome (DINO) trial [44], Smithers et al. [45] evaluated whether administering preterm infants human milk with a high DHA content would influence language and behavior at 26 months and 3–5 years. The DINO trial included infants born <33 weeks gestation fed human milk containing 1 % of total fatty acids as DHA (high DHA-group, $n=322$) or 0.3% DHA (control group, $n=335$). Lactating mothers assigned to the high-DHA group were administered 900 mg of DHA from DHA-rich tuna oil capsules per day or a placebo. Mothers whose infants were allocated to the control group were given six 500 mg placebo soy oil capsules that did not change the fat content of their milk. The initial results at 18 months of age, based on data from the Bayley Mental Development Index (MDI), indicated that the MDI score among girls fed the high-DHA milk was higher than that in the control group. Post hoc analysis indicated that fewer infants in the high-DHA group had significantly delayed mental development compared with the control. Results from the follow-up study ($n=143$) did not indicate any differences between groups on scores for language development or behavior at 26 months and 3–5 years of age [45]. The authors speculated that it may be more difficult to detect differences in development in childhood when a control group is used that provides an adequate amount of DHA. Most other trials that have considered the effects of DHA supplementation during pregnancy and/or lactation have used infant formulas without DHA as a control.

Healthy pregnant women from Spain, Germany, and Hungary were randomly assigned to receive either fish oil (FO, 500 mg/day DHA + 150 mg/day EPA, $n=43$), 5-methyltetrahydrofolate (MTHF, 400 μg/day, $n=40$), both (FO+MTHF, $n=37$), or placebo ($n=47$) from week 20 of gestation until delivery [46]. LCPUFA levels in plasma and erythrocyte phospholipids were measured in maternal blood at 20 and 30 weeks of gestation and in cord blood at delivery. Neurodevelopment was evaluated using the Hempel examination at 4 years of age and the Touwen examination at 5.5 years of age. Neurological findings were also summarized with the neurological optimality score (NOS) by assessing performance on 56 items of the neurological examination. Full-term, healthy infants were included in the study. Women were encouraged to breastfeed, but when formula was used it contained 0.5 % of total fatty acids as DHA and 0.4 % as ARA. Infants in the placebo or MTHF groups received formula

free of DHA and ARA. The results indicated that the odds of children with the maximal NOS increased with every unit increment in cord blood level of DHA at delivery. The investigators concluded that higher levels of DHA in fetal and maternal blood were associated with better neurodevelopment performance of children at 5.5 years of age.

Jensen et al. [41] reported that formerly breastfed children whose mothers received DHA supplementation of 200 mg/day for 4 months postpartum had a significantly higher mean score on the Bayley Psychomotor Developmental Index at 30 months of age than children whose mothers received a placebo. In a follow-up study at 5 years of age, measures of gross and fine motor function, perceptual/visual motor function, attention, executive function, verbal skills, and visual function were evaluated [47]. The results indicated that children whose mothers received DHA ($n=60$) compared with placebo ($n=59$) performed significantly better on the Sustained Attention Subscale of the Leiter International Performance Test, but no statistically significant differences between groups were observed on the other neuropsychological tests. The authors concluded that DHA supplementation during pregnancy and early infancy with an adequate amount of DHA may confer long-term neurodevelopmental advantages.

Finally, Danish mothers with low fish intake (below the population median: fish intake of 12.3 ± 8.2 g/day and less than 0.4 g/day of n-3 PUFA) were randomly assigned to a fish oil supplementation group (620 mg EPA, 790 mg DHA, $n=36$) or placebo ($n=28$) [48]. Women in the highest quartile of the population for fish intake (fish intake of 55.2 ± 26.7 g/day or 0.82 g/day of n-3 PUFA) served as a high fish intake reference group ($n=34$). Nine-month-old children who participated in a previous study were invited to participate in a 7-year follow-up study [49]. The initial study at 9 months of age used The Infant Planning Test to assess means-end problem solving ability. For the 7-year follow-up study ($n=98$), neurodevelopment was evaluated using measures of processing speed, the Stroop Test, and Strength and Difficulties Questionnaires. No differences were found between groups on the means-end task at 9 months of age and no treatment effect was evident for the neurodevelopmental scores at 7 years of age. To explain the lack of statistically significant findings, the authors noted that the sample size was probably too small to detect the small effect. Further, the population considered is atypical with respect to fish consumption. Danish people have a relatively high intake of n-3 LCPUFA compared to those considered in other studies that investigated the relationship between maternal LCPUFA supplementation and cognitive functions in infants and/or children [48].

Intervention Studies of LCPUFA Supplementation and Neurodevelopment Outcomes in Infants

The interventional studies of LCPUFA supplementation and neurodevelopmental outcomes in preterm and term infants are listed in Table 26.3. Two analyses were found in the literature that considered the effect of supplementing human milk with LCPUFA on cognitive development in low-birth-weight infants [50, 51]. One study evaluated variations in heart rate (HR) measures during the first half year of life in healthy term infants who were either breastfed or fed formula with or without DHA [52]. This study provided neurodevelopmental data based on Bayley Mental and Motor Scales and Auditory Comprehension and Expressive Communication Scales to evaluate language development. Two other studies considered neurodevelopmental outcomes following LCPUFA supplementation of infant formula [53, 54].

In a randomized, double-blind, placebo-controlled study among very-low-birth-weight infants (<1,500 g), 32 mg of DHA and 31 mg of ARA was added to 100 mL of human milk starting at one week after birth ($n=68$) until discharge from the hospital (~9 weeks) [50]. The control group received human milk without DHA and ARA ($n=73$). The added DHA and ARA oil was sonicated into human milk and given to the infants by gavage. Cognitive development was assessed at 6 months of age using

Table 26.3 Randomized, controlled trials of LCPUFA supplementation

			Supplementation		Functional measurements: age at assessment	Effects of supplementation	
Author (Year)	Location	*N* (enrolled)	Duration	Dose		Functional	Biochemical DHA status
Henriksen et al. [50]	Norway	141 preterm infants	1 week after birth until discharge (~9 weeks)	I1: 6.9 % DHA (32 mg) + 6.9 % ARA (31 mg) C:0 % DHA + 0 % ARA	ASQ, ERP: 6 months	↑ ASQ scores in I vs. C ($p<0.05$) ↑ amplitudes in ERP in I vs. C ($p<0.05$)	↑ in I infants ↓ in C infants
Westerberg et al. [51]	Norway	141 VLBW infants	1 week after birth until discharge (~9 weeks)	I: 0.5 mL oil (32 mg DHA + 31 mg ARA) C: Soy oil w/out DHA + ARA	Bayley MDI, ASQ: 20 months	None	None
Pivik et al [52]	USA	102 infants	Enrollment until 12 months of age	I1: Breast fed	BSID, PLS: 3 and 6 months	↑ BSID and PLS scores in I3 vs. all other groups at 3 month assessment ($p<0.05$)	N/A
				I2: Milk formula fed I3: Soy formula w/ DHA C: Soy formula w/out DHA		None at 6 month assessment	
de Jong et al. [53]	The Netherlands	474 infants	2 months	I1: Breast fed I2: LCPUFA-supplemented formula (0.3 % DHA + 0.45 % ARA) C: Standard formula	TE: 9 years	↓ NOS scores in TE in I2 and C vs. I1 ($p<0.05$)	N/A
Drover et al. [54]	USA	181 infants	12 months	I1: 0.32 % DHA (17 mg/100 kcal) + 0.64% ARA I2: 0.64 % DHA (34 mg/100 kcal) + 0.64 % ARA I3: 0.96 % DHA (54 mg/100 kcal) + 0.64 % ARA C: 0 % DHA + 0 % ARA	BSID II: 18 months ± 2 weeks	↑ MDI scores in combined I1, I2, I3 vs. C ($p<0.05$) ↑ Language scores in combined I1, I2, I3 vs. C ($p<0.05$)	N/A

ARA arachidonic acid; *ASQ* Ages and Stages Questionnaire; *BSID* Bayley Scales of Infant Development; *C* control; *DHA* docosahexaenoic acid; *ERP* Event-Related Potentials; *I* intervention; *MDI* Mental Development Index; *N/A* not applicable; *NOS* Neurological Optimality Score; *PLS* Preschool Language Scales; *TE* Touwen examination; *VLBW* very low birth weight (<1,500 g); $p<0.05$ = significant

the Ages and Stages Questionnaire (ASQ) and event-related potentials, electrophysiological recordings related to recognition memory. There were no differences in the number of adverse events or growth between the two treatment groups. The LCPUFA group performed significantly better on the problem-solving subset of the ASQ compared with the control. Additionally, compared with the control group, the LCPUFA group had better recognition memory based on the event-related potential data; these infants discriminated better between familiar and unfamiliar objects.

The same cohort of infants included in the study conducted by Henriksen et al. [50] (see above) was followed to 20 months of age [51]. Some loss due to follow-up contributed to fewer infants in the trial ($n=44$ in the LCPUFA group and 48 in the control group). Attention capacity was evaluated by two "free-play" sessions. General cognitive functions were assessed by the Bayley Mental Development Index (MDI) and the ASQ. Results indicated that LCPUFA supplementation had a positive effect on functions related to attention. No significant differences were observed between the two groups on the MDI and ASQ. However, plasma DHA levels at discharge correlated positively with "Sustained Attention" in the free-play sessions and the MDI. The investigators noted that neuro-regulatory dysfunctions at this early age, especially those related to attention, may be associated with later developmental process problems. LCPUFA supplementation appears to enhance development of the executive part of the infant's brain [51]. However, further studies are needed to determine the long-term effects of LCPUFA on sustained attention.

In a small study to investigate variations in resting HR during the first 6 months of life, full-term infants were either breastfed ($n=31$) or fed a commercially available formula with DHA and ARA (milk-based, $n=29$; soy-based, $n=30$) or without DHA and ARA (soy-based, $n=12$) [52]. Most of the infants (72 %) were fed formula with higher concentrations of DHA and ARA (DHA: 0.32 %, ARA: 0.64 % vs. DHA: 0.15 %, ARA: 0.40%). Infants remained on the selected feeding through 12 months of age. Secondary neurodevelopment outcome measures included results from the Bayley Mental and Motor Scales and Auditory Comprehension and Expressive Communication Scales to evaluate language development. There was no treatment effect on measures of neurodevelopment and language acquisition. All groups showed developmental progression throughout the study period. This study did not confirm the previous reports of slow HR in breastfed infants relative to those who were formula-fed [55]. However, infants fed the diet without DHA and ARA had a higher HR and lower values for HR variability than those observed in the other treatment groups. The investigators suggested that this cardiovascular-related finding indicates reduced parasympathetic tone in infants in the formula group without DHA and ARA. Infants with higher levels of parasympathetic activities typically show increased sustained attention and processed information more quickly [56]. Although infants fed the diet without DHA and ARA had a higher HR and lower values for HR variability than those observed in the other treatment groups, they scored in the normal range on measures of neurodevelopment and language acquisition. The small sample size and the fact that the volume of human milk consumed was not measured were limitations of the study and made it more difficult to detect treatment effects.

In a double-blind, randomized controlled trial, healthy, term infants were fed standard formula without LCPUFAs (control group, $n=169$) or a LCPUFA-supplemented formula ($n=146$) [53, 57, 58]. A breastfed group ($n=159$) served as a reference. The LCPUFA-fortified formula contained 0.30 % by weight of DHA and 0.45 % by weight of ARA. The duration of supplementation was 2 months. In the initial study, neurodevelopment was assessed at 3 months (quality of general movements, GMs) and at 18 months of age (Hemple Examination and Bayley Scales) [57, 58]. At 3 months of age, infants in the control group had significantly more mildly abnormal GMs than did infants in the LCPUFA-supplemented group or breastfed group [57]. At 18 months of age, scores of neurodevelopment were not significantly different between groups [58]. A follow-up study was conducted when children were 9 years of age using the Touwen Examination which provided a NOS (see above) [53]. The NOS did not differ between formula groups, but children who were breastfed showed significantly fewer signs of fine manipulative dysfunction than those fed formula. The authors pointed

out that a major limitation of the follow-up study was its attrition. Over the 9-year period, the attrition rate was 28 %. There was a selective loss of boys and children with worse cognitive development at 18 months in the LCPUFA-supplemented group. The selected attrition probably diminished the ability to detect any potential benefits of LCPUFA supplementation.

Finally, in a randomized, controlled clinical trial with multiple dietary levels of DHA (Control: 0 %; 0.32 %; 0.64 %; or 0.96 %) full-term infants ($n = 181$) were enrolled at 1–9 days of age and fed the assigned formulas until 12 months of age [54]. All formulas contained 0.64 % of ARA. Cognitive function was evaluated in 131 children at 18 months of age using the Bayley Scales of Infant Development. Results indicated no diet group differences on the Bayley Scales, but when the scores of children who received the DHA-fortified formulas were combined and compared to the control, children in the DHA-fortified group had a significantly higher score on the Mental Development Index (MDI) (104 vs. 98, $p < 0.02$). The authors concluded that DHA concentration of at least 0.32 % in infant formula confers enhanced neurocognitive benefits at 18 months.

Discussion and Conclusions

There is plausible evidence from both well-designed epidemiological and maternal supplementation studies (during pregnancy and/or lactation) that supports an important role for LCPUFAs, particularly DHA, in the neurodevelopment of infants and children. Some of these studies have demonstrated benefits that persist to 7 years of age. It appears that DHA supplementation initiated early in life either through placental transfer or during infant feeding (breastfeeding or infant formula fortified with LCPUFAs) provides long-term neurocognitive benefits. This may be especially important for infants born prematurely.

One of the intervention studies of very-low-birth-weight infants [50, 51] used a novel technique to add DHA and ARA to human milk. The added LCPUFA oil was sonicated into human milk and given to infants by gavage. The sonication method facilitated dispersal of the oil into human milk thereby enhancing its bioavailability. The intervention studies conducted by Henriksen et al. [50], Westerberg et al. [51], and Drover et al. [54] also supported the hypothesis that DHA and ARA have specific functions related to memory and problem-solving [59]. Using tests such as the Events Related Potentials that measures recognition memory [50] or the Bayley Motor Development Index that evaluates memory, problem solving, discrimination, and language skills indicate that the choice of endpoint measurements is crucial to identify clinically relevant findings related to LCPUFA supplementation. An important advantage of using tests that measure recognition memory is that they are stronger predictors of later IQ than other traditional tests used to evaluate different domains of neurodevelopment [60].

The reasons that some studies failed to show a statistically significant association between LCPUFA intake and better neurodevelopmental performance may have been related to limitations of study design. In the present review, many studies included small samples sizes that diminished the statistical power needed to detect differences between treatment groups [33, 48, 52]. Other studies were limited due to the lack of an adequate control [45], large attrition rates through time [53], and a ceiling effect [29, 36].

Recent consensus statements by expert panels including the Perinatal Lipid Metabolism Organization (PeriLip) [61], the Early Nutritional Programming Group (EARNEST) [61], the European Food Safety Authority [62], and the Food and Agricultural Organization of the United Nations [63] have recommended that pregnant and lactating women should aim to achieve an average dietary intake of at least 200 mg DHA/day. As discussed in these consensus reports, intakes of up to 1 g/day of DHA or 2.7 g/day of n-3 PUFA have been used in RCTs without significant adverse effects. Women of childbearing age should aim to consume one or two portions of sea fish per week, including oily fish. The expert panels indicate that the precursor of DHA, ALA, is far less effective in providing DHA than preformed DHA.

Presently, it is unclear whether a certain level or threshold of LCPUFA supplementation must be reached before a statistically significant, positive effect on neurocognitive development in infancy and childhood can be detected. It is also difficult to reach consensus on the duration of supplementation in infancy that is necessary to produce a cognitive change. Drover et al. [54] indicated that supplementation with LCPUFA for more than 6 months increases the likelihood of observing beneficial effects on cognitive function in infants. A DHA concentration of 0.32 % of total fatty acids during the first year of life appears adequate to improve cognitive function during infancy [54]. With respect to ARA levels, no study to date has investigated the effects that ARA supplementation alone has on neurocognitive development. Although one study of preterm infants demonstrated that a DHA-supplemented formula without ARA resulted in higher MDI scores and improved visual attention compared to a control group fed traditional formula [64] another study [65] reported that using an infant formula with DHA alone had a negative effect on growth and body composition (fat-free mass) in low-birth-weight infants. The majority of studies of preterm and term infants have demonstrated that ARA in a DHA-supplemented infant formula is critical for growth [66–69]. Up to 0.64% of ARA of total fatty acids is generally recognized as safe and is routinely included in commercially available infant formulas in the United States and elsewhere.

The type of DHA used may also affect neurocognitive function in infants and childhood. In the United States, the majority of studies that have considered both neurocognitive function and growth and development have used infant formulas for preterm and term infants that contain DHA obtained from single cell microalgae. Outside the United States, DHA from fish oil [42, 44] or eggs [70, 71] have been considered. This is noteworthy because only DHA from single cell microalgae has been shown to enhance neurodevelopment in both preterm [50, 51, 72] and term infants [54, 73]. The source of the oil may be important because it also positively affects growth. Clandinin et al. [72] have shown that in a study of preterm infants ($n = 361$) both body weight at 118 weeks of age and length at 79 or 92 weeks of age were greater in preterm infants fed a formula containing DHA from microalgae compared with those fed DHA from tuna oil. Additionally, for both weight and length, there were no differences between breastfed infants and those fed DHA from microalgae. The possibility that DHA derived from microalgae or from fish oil may have differing effects on cognitive development is difficult to determine; the effects also might be tissue specific [54]. Infant formulas currently marketed in the United States are virtually EPA-free, while a number of formulas available outside the United States contain EPA where fish oil is used as the source of DHA. Based on findings from a number of RCTs in infants fed formulas supplemented with fish oils, the European experts and authorities [19, 74, 75] have recommended that the EPA content be limited to no more than the DHA content. The safety profile of LCPUFA supplements added to infant formulas has been extensively studied over the years since their introduction and, to date, no pattern suggesting a safety concern has been identified. The Pediatric Nutrition Handbook [76] of the American Academy of Pediatrics acknowledges that the LCPUFA additives "are safe."

Maternal nutrition plays a critical role in influencing fetal growth and birth outcomes [77]. It represents a modifiable risk factor of great public health importance in the effort to promote optimal birth outcomes and infant growth and development. The epidemiological, supplementation, and intervention studies considered in the present review have generally shown promising, positive effects of LCPUFA supplementation on neurocognitive development in infants. Some of these neurocognitive benefits persist into early childhood. While RCTs provide the best evidence of causal relationships, some often have design flaws that limit the likelihood of detecting a significant effect. All RCTs, when practical, should include a suitable control group and adequate statistical power to detect subtle effects of cognitive changes in subjects who are generally healthy at the time of enrollment. To increase the likelihood of observing a significant association between LCPUFA supplementation and a cognitive outcome, it may be necessary to consider subjects with poor nutritional status or those with initially poorer neurocognitive status who can most benefit from LCPUFA supplementation. Efforts that promote good maternal and infant nutrition should continue in order to achieve optimal nutritional health.

References

1. Innis SM. Dietary omega 3 fatty acids and the developing brain. Brain Res. 2008;1237:35–43.
2. Martinez M. Tissue levels of polyunsaturated fatty acids in early human development. J Pediatr. 1992;120:129–38.
3. O'Brien JS, Sampson EL. Fatty acid and fatty acid aldehyde composition of the major brain lipids in normal human gray matter, white matter, and myelin. J Lipid Res. 1965;6:545–51.
4. Salem Jr N. Omega-3 fatty acids: molecular and biochemical aspects. In: Spiller J, Scala GA, editors. Current topics in nutrition and disease. New York: Liss; 1989. p. 109–228.
5. Dobbing J. Lasting deficits and distortions of the adult brain following infantile undernutrition. In: World Health Organization, editor. Nutrition, the nervous system, and behaviour: proceedings of the seminar in malnutrition in early life and subsequent mental development. Washington DC: World Health Organization; Scientific Publications 251; 1972:15–23.
6. Martinez M. Polyunsaturated fatty acids in the developing brain, red cells and plasma: influence of nutrition and peroxisomal disease. World Rev Nutr Diet. 1994;75:70–8.
7. Innis SM. Essential fatty acid transfer and fetal development. Placenta. 2005;26:S70–5.
8. Hadley KB, Ryan AS, Nelson EB, et al. An assessment of dietary docosahexaenoic acid requirements for brain accretion and turnover during early childhood. World Rev Nutr Diet. 2009;99:97–104.
9. Pawlosky RJ, Hibbeln JR, Lin Y, et al. Effects of beef- and fish-based diets on the kinetics of n-3 fatty acid metabolism in human subjects. Am J Clin Nutr. 2003;77:565–72.
10. Goyens PL, Spilker ME, Zock PL, et al. Compartmental modeling to quantify alpha-linolenic acid conversion after longer-term intake of multiple tracer boluses. J Lipid Res. 2005;46:1474–83.
11. Burdge A. Alpha-linolenic acid metabolism in men and women: nutritional and biological implications. Curr Opin Clin Nutr Metab Care. 2004;7:137–44.
12. Su HM, Bernardo L, Mirmiran M, et al. Dietary 18:3n-3 and 22:6n-3 as sources of 22n:6n-3 accretion in neonatal baboon brain and associated organs. Lipids. 1999;34:S347–50.
13. Koletzko B, Larque E, Demmelmair H. Placental transfer of long-chain polyunsaturated fatty acids (LC-PUFA). J Perinat Med. 2007;35:S5–11.
14. Innis SM. Polyunsaturated fatty acids in human milk: an essential role in infant development. Adv Exp Med Biol. 2004;554:27–43.
15. Yuhas R, Pramuk K, Lien EL. Human milk fatty acid composition from nine countries varies most in DHA. Lipids. 2006;41:851–8.
16. de Groot RH, Hornstra G, van Houwellingen AC, et al. Effect of alpha linolenic acid supplementation during pregnancy on maternal and neonatal polyunsaturated fatty acid status and pregnancy outcome. Am J Clin Nutr. 2004;79:251–60.
17. Ponder DL, Innis SM, Benson JD, et al. Docosahexaenoic acid status of term infants fed breast milk or infant formula containing soy oil or corn oil. Pediatr Res. 1992;32:683–8.
18. Ratnayake WM, Galli C. Fat and fatty acid terminology, methods of analysis and fat digestion and metabolism: a background review paper. Ann Nutr Metab. 2009;55:8–43.
19. Codex Alimentarius. Codex Standard 72 – 1981. Standard for Infant Formula and Formulas for Special Medical Purposes Intended for Infants. (Formerly CAC/RS 72–1972. Adopted as a world-wide Standard 1981.Amended 1983, 1985,1987. Revision 2007: 1–21. http://www.**codex**alimentarius. net/download/**stan**dards/288/CXS_072e. pdf. Accessed 30 June 2011.
20. Koletzko B, Demmelmair H, Schaeffer L, et al. Genetically determined variation in polyunsaturated fatty acid metabolism may result in different dietary requirements. In: German JB, Lonnerdal B, Bier DM, editors. Personalized nutrition for the diverse needs of infants and children. Nestlé nutr workshop ser pediatr program, vol. 62. Basel: Nestec Ltd, Vevey/Karger AG; 2008. p. 35–49.
21. Koletzko B, Lattka E, Zeilinger S, et al. Genetic variants of the fatty acid desaturase gene cluster predict amounts of red blood cell docosahexaenoic and other polyunsaturated fatty acids in pregnant women: findings from the Avon Longitudinal Study of Parents and Children. Am J Clin Nutr. 2011;93:211–9.
22. Rzehak P, Heinrich J, Klopp N, et al. Evidence for an association between genetic variants of the fatty acid desaturase I fatty acid desaturase 2 (FADS1 FADS2) gene cluster and the fatty acid composition of erythrocyte membranes. Br J Nutr. 2009;101:20–6.
23. Xie L, Innis SM. Genetic variants of the FADS1 FADS2 gene cluster are associated with altered (n-6) and (n-3) essential fatty acids in plasma and erythrocyte phospholipids in women during pregnancy and in breast milk during lactation. J Nutr. 2008;138:2222–8.
24. Mathias RA, Sergeant S, Ruczinski I, et al. The impact of FADS genetic variants on omega-6 polyunsaturated fatty acid metabolism in African Americans. BMC Genet. 2011;12:50. doi:10.1186/1471-2156-12-50.

25. Beyerlein A, Hadders-Algra M, Kennedy K, et al. Infant formula supplementation with long-chain polyunsaturated fatty acids has no effect on Bayley Developmental scores at 18 months of age—IPD meta-analysis of 4 large clinical trials. J Pediatr Gastroenterol Nutr. 2010;50:79–84.
26. Hoffman DR, Boettcher JA, Diersen-Schade DA. Toward optimizing vision and cognition in term infants by dietary docosahexaenoic acid and arachidonic acid supplementation: a review of randomized controlled trials. Prostaglandins Leukot Essent Fatty Acids. 2009;81:151–8.
27. SanGiovanni JP, Parra-Cabrera S, Colditz GA, et al. Meta-analysis of dietary essential fatty acids and long-chain polyunsaturated fatty acids as they relate to visual resolution acuity in healthy preterm infants. Pediatrics. 2000;105:1292–8.
28. Bakker EC, Hornstra G, Blanco CE, et al. Relationship between long-chain polyunsaturated fatty acids at birth and motor function at 7 years of age. Eur J Clin Nutr. 2009;57:89–95.
29. Mendez MA, Torrent M, Julvez J, et al. Maternal fish and other seafood intakes during pregnancy and child neurodevelopment at age 4 years. Public Health Nutr. 2009;12:1702–10.
30. Mahaffey KR. Fish and shellfish as dietary sources of methylmercury and the omega-3 fatty acids, eicosapentaenic acid and docosahexaenoic acid: risks and benefits. Environ Res. 2004;95:414–28.
31. Tanaka K, Kon N, Ohkawa N, et al. Does breastfeeding in the neonatal period influence the cognitive function of very-low-birth-weight infants at 5 years of age? Brain Dev. 2009;31:288–93.
32. Gale CR, Marriott LD, Martyn CN, et al. Breastfeeding, use of docosahexaenoic acid-fortified formulas in infancy and neuropsychological function in childhood. Arch Dis Child. 2010;95:174–9.
33. Keim SA, Daniels JL, Siega-Riz AM, et al. Breastfeeding and long-chain polyunsaturated fatty acid intake in the first 4 post-natal months and infant cognitive development: an observational study. Matern Child Nutr. 2012;8:471–82.
34. Cohen JT, Bellinger DC, Connor WE, et al. A quantitative analysis of prenatal intake of n-3 polyunsaturated fatty acids and cognitive development. Am J Prev Med. 2005;29:366–74.
35. Hibbeln JR, Davis JM, Steer C, et al. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. Lancet. 2007;17:578–85.
36. Rioux FM, Bélanger-Plourde J, LeBlanc CP, et al. Relationship between maternal DHA and iron status and infants' cognitive performance. Can J Diet Pract Res. 2011;72:e140–6.
37. Ryan AS, Nelson EB. Assessing the effect of docosahexaenoic acid on cognitive functions in healthy, preschool children: a randomized, placebo-controlled, double-blind study. Clin Pediatr. 2008;47:355–62.
38. Dziechciarz P, Horvath A, Szajewska H. Effects of n-3 long-chain polyunsaturated fatty acid supplementation during pregnancy and/or lactation on neurodevelopment and visual function in children: a systematic review of randomized controlled trials. J Am Coll Nutr. 2010;29:443–54.
39. Dunstan JA, Simmer K, Dixon G, et al. Cognitive assessment of children at age 2(1/2) years after maternal fish oil supplementation in pregnancy: a randomized controlled trial. Arch Dis Child Fetal Neonatal Ed. 2008; 93:F45–50.
40. Judge MP, Harel O, Lammi-Keefe CJ. Maternal consumption of a docosahexaenoic acid-containing functional food during pregnancy: benefit for infant performance on problem-solving but not on recognition memory tasks at age 9 mo. Am J Clin Nutr. 2007;85:1572–7.
41. Jensen CL, Voigt RG, Prager TC, et al. Effects of maternal docosahexaenoic acid intake on visual function and neurodevelopment in breastfed term infants. Am J Clin Nutr. 2005;82:125–32.
42. Makrides M, Gibson RA, McPhee AJ, et al. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. JAMA. 2010;304:1675–83.
43. Oken E, Belfort MB. Fish, fish oil, and pregnancy. JAMA. 2010;304:1717–8.
44. Makrides M, Gibson RA, McPhee AJ, et al. Neurodevelopmental outcomes of preterm infants fed high-dose docosahexaenoic acid: a randomized controlled trial. JAMA. 2009;301:175–82.
45. Smithers LG, Collins CT, Simmonds LA, et al. Feeding preterm infants milk with a higher dose of docosahexaenoic acid than that used in current practice does not influence language or behavior in early childhood: a follow-up study of a randomized controlled trial. Am J Clin Nutr. 2011;91:628–34.
46. Escolano-Margarit MV, Ramos R, Beyer J, et al. Prenatal DHA status and neurological outcome in children at age 5.5 years are positively associated. J Nutr. 2011;141:1216–23.
47. Jensen CL, Voigt RG, Llorente AM, et al. Effects of early maternal docosahexaenoic acid intake in neurological status and visual acuity at five years of age of breast-fed term infants. J Pediatr. 2010;157:900–5.
48. Cheatham CL, Nerhammer AS, Asserhøj M, et al. Fish oil supplementation during lactation: effects on cognition and behavior at 7 years of age. Lipids. 2011;46:637–45.
49. Lauritzen L, Jorgensen MH, Olsen SF, et al. Maternal fish oil supplementation in lactation: effect on developmental outcome in breast-fed infants. Reprod Nutr Dev. 2005;45:535–47.
50. Henriksen C, Haugholt K, Lindgren M, et al. Improved cognitive development among preterm infants attributable to early supplementation of human milk with docosahexaenoic acid and arachidonic acid. Pediatrics. 2008;121:1137–45.

51. Westerberg AC, Schei R, Henriksen C, et al. Attention among very low birth weight infants following early supplementation with docosahexaenoic and arachidonic acid. Acta Paediatr. 2011;100:47–52.
52. Pivik RT, Dykman RA, Hongkui H, et al. Early infant diet and omega-3 fatty acid DHA: effects on resting cardiovascular activity and behavioral development during the first half-year of life. Dev Neuropsychol. 2009;34:139–58.
53. de Jong C, Kikkert HK, Fidler V, et al. The Groningen LCPUFA study: no effect of postnatal long-chain polyunsaturated fatty acids in healthy term infants on neurological condition at 9 years. Br J Nutr. 2010;104:566–72.
54. Drover JR, Hoffman DR, Castañeda YS, et al. Cognitive function in 18-month-old term infants of the DIAMOND study: a randomized, controlled clinical trial with multiple dietary levels of docosahexaenoic acid. Early Hum Dev. 2011;87:223–30.
55. Massin MM, Withofs N, Ravet F. The influence of fetal and postnatal growth on heart rate variability in young infants. Cardiology. 2001;95:80–3.
56. Reynolds GD, Richards JE. Infant heart rate: a developmental psychophysiological perspective. In: Schmidt LA, Segalowitz SJ, editors. Developmental psychophysiology. Cambridge, UK: Cambridge; 2007. p. 106–17.
57. Bouwstra H, Dijck-Brouwer J, Wildeman JAL, et al. Long-chain polyunsaturated fatty acids have a positive effect on the quality of general movements of healthy term infants. Am J Clin Nutr. 2003;78:313–8.
58. Bouwstra H, Dijck-Brouwer J, Boehm G, et al. Long-chain polyunsaturated fatty acids and neurological developmental outcome at 18 months in healthy term infants. Acta Paediatr. 2005;94:26–32.
59. Willatts P, Forsyth JS. The role of long-chain polyunsaturated fatty acids in infant cognitive development. Prostaglandins Leukot Essent Fatty Acids. 2000;63:95–100.
60. McCall RB, Carriger MS. A meta-analysis of infant habituation and recognition memory performance as predictors of later IQ. Child Dev. 1993;64:57–79.
61. Koletzko B, Cetin I, Brenna T, for the Perinatal Lipid Intake Working Group. Dietary fat intakes for pregnant and lactation women. Br J Nutr 2007;98:873–7
62. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific opinion on dietary reference values for fats, including saturated fatty acids, polyunsaturated fatty acids, monosaturated fatty acids, *trans* fatty acids, and cholesterol. EFSA Journal. 2010;8:1461.
63. Food and Agricultural Organization of the United Nations. Fats and fatty acids in human nutrition: report of an expert consultation. FAO Food and Nutrition Paper 91. Rome: Food and Agricultural Organization of the United Nations; 2010:77–85.
64. Carlson SE, Werkman SH, Peeples JM, et al. Long-chain fatty acids and early visual and cognitive development of preterm infants. Eur J Clin Nutr. 1994;48:S27–30.
65. Ryan AS, Montalto MB, Groh-Wargo S, et al. Effect of DHA-containing formula on growth of preterm infants at 59 weeks of postmenstrual age. Am J Hum Biol. 1999;11:457–67.
66. Carlson SE, Werkman SH, Peeples JM, et al. Arachidonic acid status correlates with first year growth in preterm infants. Proc Natl Acad Sci. 1993;90:1073–7.
67. Diersen-Schade DA, Hansen JW, Harris CL, et al. Docosahexaenoic acid plus arachidominc acid enhance preterm infant growth. In: Riemersma RA, Armstrona R, Kelly W, Wilson R, editors. Essential fatty acids and eicosanoids: invited papers from the Fourth International Congress. Champaign, IL: AOCS Press; 1998. p. 123–7.
68. Desci T, Koletzko B. Growth, fatty acid composition of plasma lipid classes, and plasma retinol and α-tocopherol concentrations in full-term infants fed formula enriched with ω-6 and ω-3 long-chain polyunsaturated fatty acids. Acta Paediatr. 1995;84:725–32.
69. Makrides M, Neumann MA, Simmer K, et al. Dietary long-chain polyunsaturated fatty acids do not influence growth of term infants: a randomized clinical trial. Pediatrics. 1999;104:468–75.
70. Lucas A, Stafford M, Morley R, et al. Efficacy and safety of long-chain polyunsaturated fatty acid supplementation of infant formula milk: a randomized trial. Lancet. 1999;354:1948–54.
71. Fewtrell MS, Morley R, Abbott RA, et al. Double-blind, randomized trial of long-chain polyunsaturated fatty acid supplementation in formula fed to preterm infants. Pediatrics. 2002;110:73–82.
72. Clandinin MT, Van Aerde JE, Merkel KL, et al. Growth and development of preterm infants fed infant formulas containing docosahexaenoic acid and arachidonic acid. J Pediatr. 2005;146:461–8.
73. Birch EE, Garfield S, Hoffman DR, et al. A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants. Dev Med Child Neurol. 2000;42:174–81.
74. Koletzko B, Lien E, Agostoni C, et al. The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. J Perinat Med. 2008;36:5–14.
75. Committee E. Commission Directive 2006/141/EC on infant formulae and follow-on formulae and amending directive 1999/21/EC. Off J Eur Union. 2006;L401:401–33.
76. Kleinman RE, editor. Nutrition handbook. 6th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008. p. 364–86.
77. Abu-Saad K, Fraser D. Maternal and birth outcomes. Epidemiol Rev. 2010;32:5–25.

Chapter 27
Obesity in Infancy and Childhood: Diagnosis, Incidence and Strategy for Change

Ruth M. Ayling

Key Points

- There is no clear diagnostic cut off or definition of obesity in infants and young children leading to differences in estimates of prevalence.
- The risk to future health of obesity in infancy and young children is not yet completely clear. However optimizing factors likely to prevent obesity and benefit of other aspects of health is to be recommended from early life.
- Specific treatment of obesity in infants and young comprises dietary and lifestyle advice. Appropriate public health measures could further influence such strategies.

Keywords Obesity • Body weight • Body mass index • Infant obesity • Childhood obesity

There is no definitive definition of obesity for us in infants and young children. It can be defined in terms of body mass index but lack of standardization of the cut-offs used has lead to differences in terminology and variations in prevalence.

The majority of obesity in infants and children is primary, caused by a calorific intake greater than expenditure, although rare secondary causes exist. Adverse effects of obesity have been documented in children and obesity in early life increases the likelihood of clustering of cardiovascular risk factors.

Many adults are obese as children but the tracking of obesity from very early life is less clear so the usefulness of early screening programs is not definitively proven. A preventative strategy to optimize factors likely to minimize obesity and promote health from very early life is appropriate. Treatment of obesity in young children involves mainly dietary and lifestyle measures. Public health measures could also be used to alter food supply trends and moderate lifestyle factors and so influence the balance of calorific intake and expenditure

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Definition and Diagnosis

Obesity is an excess of body fat but no diagnostic cut off or definition exists for use in infants and young children. Mean body fat percentiles of how developmental changes have been derived from bioelectrical impedance analysis and exist for US children aged >12 years [1] and percentile curves are available for UK children aged 5–18 years [2]. However, it is difficult to measure body fat easily and with reasonable accuracy or precision and an alternative definition is required for ease of use in clinical and epidemiological settings.

Obesity tends to be more commonly described in terms of the body mass index (BMI) which is calculated as weight (in kg)/[height (in m)]^2. BMI does not measure body fat directly but correlates with direct measurements of body fat, for example, by underwater weighing and in adults is related to health outcomes. In adults a BMI of 25–29.9 is defined as overweight and ≥30 as obese [3]. BMI changes with age and differs with gender. BMI tends to be similar in males and females during childhood but is higher amongst females in adolescence. BMI increases from birth to around 1 year then declines until around age six, with a subsequent increase throughout childhood and adolescence. BMI reflects both fat and fat-free components of body weight and populations differ in their percentage fat mass and its distribution. BMI values obtained should therefore always be interpreted using centile charts that describe population reference data or by calculation of a Z score or SD score relative to this data. However, as BMI does not measure fat directly there has been variation in the cut-offs used to define obesity in infants and children.

In UK the 1990 growth charts in standard use are based on data from 1978 to 1990, from birth to 23 years involving 30,000 individuals. Their authors suggested the 98th percentile (equivalent to a BMI of 29 at age 20 years) and 99.6th percentile (equivalent to a BMI of 29) as reasonable definitions of obesity and super obesity [4]. However, epidemiological studies tend to use the 85th percentile as a cut-off for overweight and the 95th for obesity [5].

In US growth charts have been produced since 1971 based on the National Health and Nutrition Examination Surveys (NHANES), although the most recent US charts were produced by the Centers for Disease Control in 2000. In 1994 a US Expert Committee recommended that children with a BMI ≥ 30 or ≥95th percentile for age and gender should be considered overweight [6]. These cut-offs were selected to provide consistency with cut-offs used in adults and because in older adolescents such cut-offs are associated with adult type pattern of risk for obesity-related disease. The committee considered those with a BMI ≥ 85th but <95th percentile to be at risk of overweight. The term obese was avoided as BMI does not specifically measure body fat. In 2005, in order to address the seriousness and urgency of childhood obesity, the Institute of Medicine recommended that those aged 2–18 years with a BMI > 30 or ≥95th percentile for age and gender (whichever is smaller) be termed obese [7]. It is now recommended that those with a BMI ≥ 85th percentile but <95th centile (or <30) are now termed overweight [8]. This change in terminology has led to confusion but that currently used is in line with the International Obesity Task Force (IOTF). The IOTF centile charts are derived from data on more than 190,000 subjects from six countries and aim to provide age and sex-specific definitions of overweight and obesity in childhood and adolescence which equate to the adult definitions of overweight (BMI ≥ 25 kg/m^2) and obese (≥30 kg/m^2).

World Health organization (WHO) growth charts are available for children aged up to 2 years and are intended to describe the growth of healthy children. A BMI-for age between 1–2 SDs suggests a child at risk for overweight, a BMI-for age of 2–3 SDs suggests overweight and a BMI-for age SD of >3 suggests obesity [9, 20].

Prevalence

It is estimated that about 43 million children under the age of 5 years are obese, about 35 million of which are in developing countries [9, 20]. However estimates of the prevalence of obesity may be subject to variation according to the cut-off or the reference standards as can be seen in Table 27.1.

Aetiology

The majority of obesity in childhood is primary and is caused by a calorific intake that is greater than expenditure. However, the relative contributions of diet and of physical and sedentary activity are unclear and may be complicated by issues such as genetic variation and assortative mating. Various risk factors have been reported to be associated with overweight and obesity (Table 27.2). There are also a number of other, rarer, causes of obesity (Table 27.3). Genetic and syndromic causes of obesity should be given particular consideration in infants and young children presenting with obesity.

Children with primary obesity tend to be tall and to have a slightly advanced bone age. Children with genetic and endocrine causes of obesity are often short with a delayed bone age and may have specific clinical features on examination, for example, red hair in pro-opiomelanocortin deficiency.

Complications

In adults and adolescents obesity has been well documented to correlate positively with risk factors for cardiovascular disease. There is as yet little evidence for this in pre-school children although obesity early in life does appear to increase the likelihood of clustering of cardiovascular risk factors. There are a number of other adverse effects of obesity which have been documented in childhood (Table 27.4).

Strategy for Change

Screening

At present there is insufficient evidence to introduce a population screening program for obesity in children [10]. However, as growth monitoring can be easily performed as part of child health checks there is the potential to obtain this information and provide feedback to parents on their children's weight status. In US mandatory BMI assessment of children in public schools and annual reporting to parents began in a single state in 2003 and has been taken up by others since [11] and it is recommended that clinicians screen children older than 6 years for obesity and offer them appropriate assistance to promote improvement in weight status [12]. There is currently insufficient evidence for screening children less than 6 years of life although rapid weight gain in the first 2 years of life has been suggested as a potential screening tool for young children at risk of becoming overweight [13].

Table 27.1 Prevalence rates (%) of overweight and obesity in children by age and country using International Obesity Task Force (IOTF) and World Health Organisation (WHO) standards [19]

	IOTF standards*						WHO standards+					
	Overweight			Obesity			BMI-for-age >2 and ≤3 SD			BMI-for-age ≥3 SD		
	2 years	3 years	4 years	2 years	3 years	4 years	2 years	3 years	4 years	2 years	3 years	4 years
Czech republic 2001* 2004+	8.5	8.3	8.2	2.1	2.0	2.0	4.4	3.7	3.9	1.1	1.1	1.5
Greece 2003–2004*	15.1	16.6	16.2	5.8	7.2	11.1	4.4	3.7	3.9	1.1	1.1	1.5
Italy 2005*	10.2	13.5	14.4	3.1	4.5	7.8	10.1	9.4	11.6	3.4	4.2	4.1
Poland 2000*	26.0	4.9	10.4	4.0	12.2	12.5	14.3		4.4		12.2	4.3
Portugal 2001*	–	15.4	16.9	–	5.1	6.2		9.6	9.1		1.2	1.4
Romania 2004*	9.2	6.8	6.7	4.5	4.6	5.1	7.1	6.4	3.0	2.2	1.6	2.5
Spain 1998–2000*	8.9	16.7	24.7	6.3	11.5	7.5	5.1	10.4	8.6	5.1	5.2	4.3
UK England 2001–2002 *	19.6	15.2	15.5	2.3	4.6	5.7	10.1	8.3	7.7	1.6	2.8	2.6
Scotland 2001–2002*	13.5	16.0	15.1	3.3	4.3	4.4	9.1	6.5	6.2	1.6	2.9	2.2

Table 27.2 Risk factors associated with the development of obesity in infants and children

Diet	Dietary fat, carbohydrate and sweetened drinks
	Missing breakfast
	Large portion size
Lifestyle	Low levels of physical activity
	Television viewing
	Residence in urban rather than rural area
	Short sleep duration
Ethnicity	Hispanic, native American, black or south Asian origin
Prenatal	Intrauterine exposure to maternal obesity
Birthweight	Small for gestation age babies who exhibit rapid catch up growth at risk of obesity in childhood
	Higher birth weight associated with overweight in adolescence

Table 27.3 Secondary causes of obesity in childhood

Genetic
Monogenic, e.g., leptin deficiency, pro-opiomelanocortin deficiency
Syndromes, e.g., Prader-Willi, Bardet-Biedl, Cohen
Endocrine
Hypothyroidism
Cushing's syndrome
Growth hormone deficiency
Pseudohypoparathyroidism
Neurological
Brain injury/trauma
After cranial irradiation
Hypothalamic obesity
Psychological
Depression
Eating disorders, e.g., binge eating
Drug induced
Anticonvulsants, e.g., sodium valproate
Glucocorticoids
Tricyclic antidepressants

Table 27.4 Adverse effects of childhood obesity

Cardiovascular	Hypertension
	Left ventricular hypertrophy
	Arteriosclerosis
Respiratory	Asthma
	Obstructive sleep apnoea
Metabolic	Insulin resistance
	Impaired glucose tolerance/diabetes
	Dyslipidemia
Gastrointestinal	Gastro-oesophageal reflux
	Non-alcoholic fatty liver disease
Orthopedic	Tibia vara
	Slipped capital femoral epiphysis
Other	Depression
	Pseudotumour cerebri
	Polycystic ovary syndrome

Prevention

Due to the association of obesity with adverse outcomes at all ages, its prevention throughout life would appear appropriate. It is known that childhood adiposity tracks into adulthood and is related to adult cardiovascular disease but it is not yet determined whether the metabolic risks associated with obesity in infancy and childhood are reversible. Certainly not all overweight infants become obese adults but there is evidence of tracking of dietary and lifestyle behaviors from childhood throughout adolescence to adulthood which can impact on health. It therefore seems sensible in infants and young children to work with parents to optimize factors that are likely to prevent obesity and may benefit some other aspect of health.

Breast feeding has been shown to offer a protective effect against the later development of obesity. It has been suggested that this is related to socio-economic factors but other possible mechanisms include allowing infants greater ownership of feeding than bottle feeding and hence enhancing self-regulation in response to hunger and satiety. Limitation of portion size is as relevant to infants as it is to older children and overfeeding of infants with formula milk should be avoided. Sugar-sweetened drinks are energy-dense and are not a necessary component of the diet of infants or young children. Physical exercise is an important component of a healthy lifestyle in older children and adults. In infants who are not yet independently mobile opportunities for prevention of obesity can by afforded by maximizing play and limiting the use of devices tending to restrict movement such as high-chairs and car seats to their intended purposes. In young children both unstructured and structured exercise are important aspects of obesity prevention. There is evidence that short sleep duration may be a risk factor for childhood obesity. It may be that this reflects an association with reduced activity. However, other suggested mechanisms include reduced opportunity for feeding and the lipolytic action of growth hormone, which is secreted during sleep.

Treatment

Whilst pharmacological and surgical options have been offered as treatments for obesity in older children and adolescents they are not generally appropriate in young children. Treatment in this age-group is essentially achieved by nutritional intervention and life-style change.

There is very little literature on the optimal nutritional therapy for weight management in young children [14]. Few clinical trials have examined the effect of diet without confounding variables such as physical activity or of any specific dietary or macronutrient strategy. Approaches to nutritional therapy tend to be adapted from those used in adults or older children, although any intervention in infants and young children is most likely to succeed if directed at the whole family.

The American Academy of Pediatrics has suggested a four staged approach to the treatment of obesity in children consisting of a program of prevention, structured weight management, multidisciplinary intervention and tertiary level care [14]. In UK, NICE Guidance recommends tailored clinical intervention for children with a BMI ≥ 91st percentile and assessment for co-morbidities if BMI ≥ 98th percentile; specific referral should be considered for children with significant morbidities and other complex needs such as learning difficulties [15]. Many would also consider obesity in children under 2 years old as an indication for specialist referral due to the increased likelihood of an underlying secondary cause.

Nutritional Therapy

Weight loss is essential in the treatment of obesity in adults and older children. However, for preschool children, in the absence of complications, the aim of treatment is prolonged weight maintenance which will lead to a reduction in BMI Z score with growth over time.

"Traffic light" diets have been used in young children. Such systems use a calorie-based exchange system with foods divided into color-coded groups according to their nutritional density [16]. Green ("go") foods such as fruit and vegetables can be eaten relatively freely and the majority of staple foods are classified as amber "eat cautiously." Red ("stop") foods include such things as highly refined carbohydrate snacks. When first devised the diet was envisaged to be used within a matrix of calorie counting with red foods limited to no more than 4 a week. In children it is particularly important o establish a framework of healthy decision making and eating choices and a prescriptive dietary regimen may prove counterproductive in this respect. Eating appropriately is as important as eating less and in young children a less rigid structure may be more useful. Nutritional advice would include consumption of regular meals and snacks paying attention to their composition. Foods with a high glycaemia index or high saturated fat content should be minimized and fruit and vegetable consumption maximized. Portion size should be realistic. General principles of nutrition management of obesity in young children are given in Table 27.5.

Lifestyle

As with obesity prevention its treatment involves healthy lifestyle advice with respect to physical activity. For infants, independent play should be encouraged. Preschool children should be given the opportunity for at least an hour of moderate activity a day. In addition to regular structured exercise such as team sports, dancing or swimming, children should be encouraged to incorporate exercise into daily activities—for example, choosing stairs and walking to school. Time spent undertaking sedentary activities such as watching television and using a computer should be minimized. Such pursuits are relatively inactive and tend to be likely associated with snacking.

Public Health Measures

Public health measures have been used effectively for a number of issues threatening health, a notable recent example being smoking. Public health measures could potentially be used to address obesity, however, unlike cigarettes, food is essential for health and the evidence base for interventions particularly in infant and childhood obesity is poorly defined. Any public health measures would therefore aim to change current food supply trends in order to encourage better health. For example, the WHO Obesity Charter [9, 20] has been accepted by governments but requires political support to be implemented.

Table 27.5 Suggested principles for the nutritional management of obesity in young children

Restrict caloric intake to achieve weight maintenance
Encourage balanced diet containing fruit, vegetables, fibre, fish and low-fat diary products
Reduce consumption of calorie-dense foods particularly snacks with high glycaemic indices or high saturated fat contents
Eliminate sweetened beverages

The rising healthcare costs of obesity are sufficient to justify prevention as a government issue. Particularly in relation to infants and children it can be argued that there is a role for such intervention in ensuring they are offered an optimum diet for later health. Possibilities for government intervention include regulating advertising, differential food taxes to promote consumption of healthier food types, changes to the physical environment such as improvements to parks and provision of guidelines for physical education and nutrition in schools.

The food industry currently facilitates obesogenic patterns of behavior. Purchase of high-fat, energy-dense foods is encouraged. The provision of food labeling detailing the fat content of food has been shown to be a useful tool in changing eating patterns [17] and in UK the Food Standards Agency has proposed a "traffic-light" front of pack labeling system for pre-packed foods [18].

The media also has a powerful impact on food choices. The type of television advertising currently aimed at children tends to promote the choice of unhealthy foods. There is potential to ensure that advertising to children contains health messages consistent with public health policies.

Conclusion

Obesity is an increasing problem amongst young children. Many adults are obese as children but the later risks to health of obesity in infants have not yet been fully determined. However, it would seem sensible to adopt a preventive strategy to optimize factors that are likely to prevent obesity and may benefit some other aspect of health throughout life and to treat young children who become obese.

References

1. Chumlea WC, Guo SS, Kuczmarski RJ, Flegal KM, Johnson CL, Heymsfield SB, Lukaski HC, Friedl K, Hubbard VS. Body composition estimates from NHANES III bioelectrical impedance data. Int J Obes Relat Metab Disord. 2002;26:1596–609.
2. McCarthy HD, Cole TJ, Fry T, Jebb SA, Prentice AM. Body fat reference curves for children. Int J Obes (Lond). 2006;30:598–602.
3. WHO. Physical status: the use and interpretation of anthropometry. Geneva: World Health Organisation, Technical Report Series; 1995. 854.
4. Cole TJ, Freeman JV, Preece MA. Body mass index reference curves for the UK, 1990. Arch Dis Child. 1995;73(1):25–9.
5. Reilly JJ, Wilson M, Summerbell CD, Wilson DC. Obesity diagnosis, prevention and treatment: evidence-based answers to common questions. Arch Dis Child. 2002;86:392–5.
6. Himes JH, Dietz WH. Guidelines for overweight in adolescent preventive services: recommendations from an expert committee: the Expert Committee on Clinical Guidelines for Overweight in Adolescent Preventive Services. Am J Clin Nutr. 1994;59:307–16.
7. Koplan JP, Liverman CT, Kraak VI, editors. Preventing childhood obesity: health in the balance. Washington, DC: National Academies Press; 2005.
8. Krebs NF, Himes JF, Jacobson D, Nicklas TA, Guilday P, Styne D. Assessment of child and adolescent overweight and obesity. Pediatrics. 2007;120:S193–228.
9. World Health Organisation Regional Office for Europe. European charter on counteracting obesity. Adopted at the WHO European ministerial conference on counteracting obesity. Istanbul. 2006 http://www.euro.who.int/Document/E89567.pdf. Accessed 25 Aug 2011.
10. Westwood M, Fayter D, Hartley S, Rithalia A, Butler G, Glasziou P, Bland M, Nixon J, Stirk L, Rudolf M. Childhood obesity: should primary school children be routinely screened? A systematic review and discussion of the evidence. Arch Dis Child. 2007;92:416–22.
11. Justus MB, Ryan KW, Rockenbach J, Ktterapalli C, Card-Higginson P. Lessons learned while implementing a legislated school policy: body mass index assessment among Arkansas' public school students. J Sch health. 2007;77:706–12.

12. US Preventative Task Force. Screening for obesity in children and adolescents: US preventive services task force recommendation statement. Pediatrics. 2010;125:361.
13. Gungor DE, Paul IM, Birch LB, Barton CJ. Risky vs. rapid growth in infancy: refining pediatric screening for childhood overweight. Arch Pediatr Adolesc Med. 2010;164:1091–7.
14. Spear BA, Barlow SE, Ervin C, Ludwig DS, Saelens BE, Schetzina KE, Taveras EM. Recommendations for treatment of child and adolescent overweight and obesity. Pediatrics. 2007;120:S254–88.
15. National Institute for Health and Clinical Excellence. Obesity CG43. London: National Institute for Health and Clinical Excellence; 2010.
16. Epstein LH, Myers MD, Raynor HA, Saelens BE. Treatment of paediatric obesity. Pediatrics. 1998;101:554–70.
17. Roefs A, Jansen A. The effect of information about fat content on food consumption in overweight/obese and lean people. Appetite. 2004;43:319–22.
18. Food Standards Agency. Front of pack nutrition labelling for pre-packaged foods sold through retail outlets in the UK. http://www.food.gov.uk/consultations/ukwideconsults/2009/fopnutritionlabelling. Accessed 25 Aug 2011.
19. Cattaneo A, Monasta L, Stamatakis E, Lionet S, Castelbon K, Frenken F, Manios Y, Moschonis G, Savva S, Zaborskis A, Rito AI, Nanu M, Vignerova J, Caroli M, Ludvigsson J, Koch FS, Serra-Majem L, Szponar L, van Lenthe F, Brug J. Overweight and obesity in infants and pre-school children in the European Union: a review of existing data. Obes Rev. 2010;11:389–98.
20. WHO. Population based prevention strategies for childhood obesity: report of a WHO forum and technical meeting. Geneva; 2009.

Chapter 28
Infant Growth and Adult Obesity: Relationship and Factors Affecting Them

Ulla Sovio, Evangelia E. Ntzani, and Ioanna Tzoulaki

Key Points

- An early life component is increasingly being recognised in the aetiology of obesity.
- Many epidemiological studies have shown that early weight gain, infant overweight and infant obesity are associated with overweight and obesity in later life.
- There is a prevailing diversity on the definitions of exposures which limits the interpretation of a postulated prognostic association between isolated infant size estimates and adult obesity.
- The available accumulated evidence in the field fails to answer important public health questions and support clinical decisions, the most important being the exact timing for overweight/obesity screening.

Keywords Infant growth • Obesity • Developmental origin of disease hypothesis • Birth size • Epidemiological methods

Introduction

Obesity reflects the energy imbalance between calorie consumption and expenditure leading to abnormal body weight with direct negative consequences on human health. Obesity is considered today a pandemic since its prevalence has more than doubled since 1980 worldwide [1]. It increases the risk of chronic diseases such as type 2 diabetes, cardiovascular disease, musculoskeletal disorders, and some cancers, and it is the fifth most important risk factor of death globally. The underlying causes

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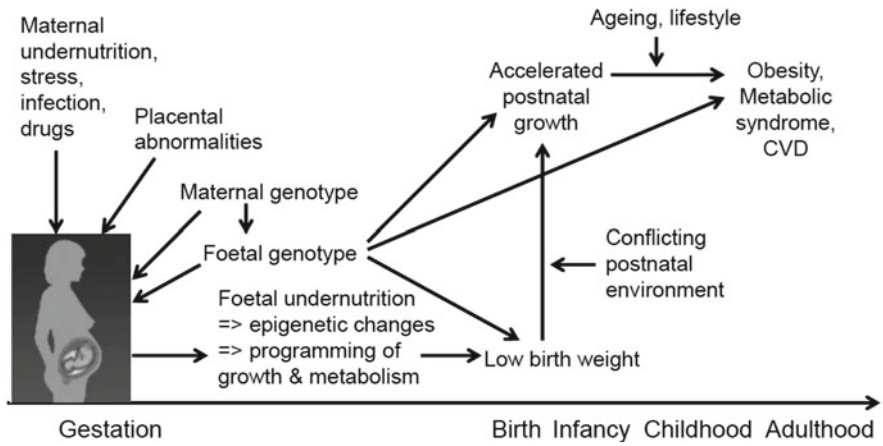

Fig. 28.1 Developmental Origins of Health and Disease (DOHaD) hypothesis. Adapted from Ozanne and Constancia [25]

contributing to the rising prevalence of obesity are complex and involve societal and environmental risk factors such as urbanisation and changing modes of work and transport as well as various individual risk factors. An early life component is increasingly being recognised in the aetiology of obesity [2, 3] being of major potential importance for public health strategies' guidance. Patterns of growth associated with low birth weight and increased weight gain in childhood, as well as low birth weight per se, have shown inverse associations with obesity and related disorders such as insulin resistance, diabetes, and cardiovascular disease in adulthood [4–7]. In addition to birth weight and childhood growth trajectories, immediate postnatal growth has received considerable attention in the medical literature. This is the period of the fastest growth in the entire life span and is a critical window of tissue and organ development wherein several regulatory mechanisms continue to develop after birth [8]. Thus, variations in this process may have long-lasting effects on health. Several studies have examined weight changes between birth and the first years of life; results have suggested that weight gain is associated with childhood, adolescent, and adult obesity and with higher levels of cardiovascular and metabolic risk factors [9, 10]. There is also evidence that increased growth velocity in first years of life is associated with obesity and metabolic outcomes in adulthood [3, 11]. However, the majority of those studies use different definitions of postnatal growth and obesity, as well as of surrogate metabolic outcomes, which poses challenges in synthesising the available evidence in order to draw firm conclusions. Here we attempt to summarise the biological basis, which may explain the association between postnatal growth with later onset of obesity. We also aim to present the main evidence from observational studies, which examine associations between postnatal growth and obesity and focus on the main methodological limitations associated with this research area. We will focus our description on human studies; however, there is a large body of literature examining early life programming in animal models.

Biologic Plausibility

The association between small size at birth and higher risk of adult disease, such as type 2 diabetes and cardiovascular, has been consistently reported [12]. The foetal origins of adult disease hypothesis was first introduced by Barker [13] and was later named Developmental Origins of Health and Disease (DOHaD) hypothesis [14] (Fig. 28.1). It can be placed within a wider framework of life course approaches to chronic disease epidemiology. In this framework, the DOHaD hypothesis has a close relationship with the critical period model that includes later life effect modifiers [15]. Here we describe hypothesis

that have been suggested to explain association between birth weight and early life growth with obesity and related disorders including type 2 diabetes and cardiovascular disease.

Hypotheses Explaining Inverse Association Between Birth Size and Adult Disease

There are two main hypotheses that have been put forward to explain the observed inverse association between small size at birth and adult disease: (1) foetal programming i.e. the thrifty phenotype hypothesis and (2) genetic susceptibility hypothesis, which proposes pleiotropic genetic effects for foetal and adult phenotypes or traits [16]. The idea of programming induced by foetal undernutrition was originally implied as an explanation behind the statistical associations between small size at birth and adult disease [13] and it is often included in the definition of the Barker or DOHaD hypothesis. The foetal programming hypothesis emphasises the environmental and the foetal insulin hypothesis the genetic influences behind the association between foetal growth and adult disease. The environmental effects may include maternal undernutrition and other maternal or placental abnormalities leading to foetal undernutrition, hormonal effects such as increased administration of natural glucocorticoids from the mother to the foetus during stress, and/or accelerated postnatal growth followed by restricted foetal growth. The foetal programming hypothesis proposes that the adaptive response of the foetus to the in utero environment at "critical periods" of development leads to permanent changes in its body structure, physiology and metabolism [13]. As an alternative mechanism, it has been suggested that pleiotropy may explain at least part of the association between the foetal and adult phenotype. In particular, the foetal insulin hypothesis proposes an insulin-resistant genotype which leads to both smaller size at birth and to an insulin-resistant phenotype in adulthood, increasing the risk of T2D and related diseases [16].

Foetal Undernutrition

The hypothesis of foetal programming due to undernutrition postulates that the adverse conditions in the intrauterine environment cause the foetus to optimise the use of energy to guarantee its survival. This kind of adaptation, allowed by developmental plasticity [17], has short-term benefits (survival of the foetus) but detrimental permanent effects to the growth and function of the tissues, which later increase the risk of obesity, type 2 diabetes and cardiovascular disease [18, 19]. However, maternal undernutrition is not common in Western societies [20] where most of the research on this topic has been done. In these countries, the function of placenta plays a more important role. However, the associations between absolute or relative measures of placental weight and type 2 diabetes and cardiovascular disease have been inconsistent [18]. Pre-eclampsia as an extreme form of placental dysfunction seems to be associated to cardiovascular disease in the mothers and a higher blood pressure in the offspring; however, the potential role of genetic factors in this association remains unclear. In their review, Jaddoe and Witteman [18] conclude that there is no strong evidence for the foetal programming hypothesis by foetal undernutrition from the existing studies.

Maternal Stress and Glucocorticoids

An increasing problem among pregnant women especially in the Western societies is social stress due to career demands, financial uncertainty and a low level of support from family [20]. Glucocorticoids belong to steroid hormones and the most important one of them in humans is cortisol. Stress during

pregnancy causes plasma glucocorticoid levels to rise in the mother. It is also known that administration of glucocorticoids during pregnancy leads to lower birth weight of the baby. The babies with decreased birth weight have increased cortisol levels throughout life, which may be explained by the programming of the function of the hypothalamic-pituitary adrenal axis (HPA), which is sensitive to glucocorticoids [21]. In particular, placental 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) enzyme inhibits glucocorticoids by converting maternal cortisol to inactive cortisone. Reduced placental 11βHSD2 is associated with both lower birth weight and higher blood pressure in later life in the offspring [22]. Studies in knockout mice support these findings [23]. It has been suggested that the molecular mechanism that underlies the programming may include epigenetic changes which could be passed on to subsequent generations without further exposure [24].

Epigenetic Modifications

In the recent years, increasing amount of research has focused on the role of epigenetics in DOHaD [25, 26]. Epigenetic modifications, including DNA methylation and histone modifications, regulate gene activity without affecting the DNA sequence. For example, in mammals, parent of origin effects on gene expression and X-chromosome inactivation in females can be observed. The early foetal period after conception has been identified as a critical window for the establishment of DNA methylation patterns, and at a later stage, tissue-specific patterns of epigenetic modifications have been shown in organisms [27]. There is an increasing body of evidence, mainly from animal models, suggesting that epigenetic changes due to early environmental factors have an important role in later disease susceptibility (see reviews of these studies in Ozanne and Constancia [25] and Gluckman et al. [26]). Imprinted genes, whose effect on gene expression is parent-specific, provide good candidates for the search for genes involved in developmental programming through epigenetic modifications. Some evidence already suggests the involvement of imprinted genes in growth and metabolism [25].

Growth Acceleration

The growth acceleration hypothesis postulates that the foetal growth restriction relative to genetic growth potential could result in compensatory postnatal growth acceleration which is responsible for the higher risk of adult disease [27]. Accelerated growth is often linked to the nutritional environment during infancy [28]. Animal studies, in which the perinatal environment can be manipulated, have reported that early life nutritional experiences different in quantity or quality of nutrition are associated with obesity and a higher metabolic rate in adulthood [8] as a result of tissue remodelling, changes in cell differentiation, organ growth, and cell signalling [3, 29–31]. Postnatal nutritional excess, has been shown associations with chronic increase in leptin levels, which is further associated with obesity [32].

Genetic Susceptibility

The foetal undernutrition, glucocorticoid and growth acceleration hypotheses all imply foetal or postnatal programming. The genetic susceptibility hypothesis has recently gained some support as an alternative hypothesis for the mechanism underlying the association between birth size and adult disease. The foetal insulin hypothesis, which specifically postulates a genotype producing small, thin

babies and insulin-resistant adults, relies on the importance of foetal insulin secretion as a key factor in foetal growth particularly in the third trimester of pregnancy [16]. The evidence for this hypothesis at the time it was presented came from studies on rare monogenic variants that were associated with both low birth weight and altered insulin secretion or resistance later in life. Twin studies examining this hypothesis have overall been inconclusive and population-based genetic association studies conducted before the genome-wide era have produced conflicting results [18]. However, recent studies have indicated that at least part of the association between low birth weight and type 2 diabetes in particular may be explained by common genetic effects [33, 34]. An age-dependent association between variation at the FTO locus which is associated with obesity and type 2 diabetes, and body mass index (BMI) in children has also been suggested [35].

Synthesis and Future Research

It remains still unclear which of the suggested mechanisms has the best explanatory power for the association between birth size and early growth and adult obesity and disease. It is likely that none of them is adequate in itself but several mechanisms operate simultaneously [16]. The role of different mechanisms may vary between different adult trait or diseases studied. Therefore, further studies on these mechanisms are warranted. It is important to design epidemiological studies in a way that allows the examination of these mechanisms in conjunction with each other. Such study design would be a prospective, population-based cohort study on a large number of subjects with a follow-up of their growth and health frequently from pregnancy until adulthood [18].

Methodological Challenges in Examining Early Life Effects on Adult Obesity

The research agenda of early life effects on adult obesity and its consequences is a complex system of associations exhibiting a spectrum of interactions ranging from completely independent to highly correlated associations. Each association represents an individual research question that is typically approached through observational studies, birth cohort studies in their majority. Delineating fundamental aspects of this system of associations will eventually lead to specific clinical research questions which have been and will be pursued through intervention-based hypothesis-testing under rigorous clinical trials' designs with the ultimate goal of the effective prevention of the long-term detrimental consequences of obesity. Deciding upon the specific association that best addresses the research question under study is a complex endeavour involving serious considerations on all study design aspects, including and not limited to the population and outcome under study and definitions thereof, as well as the early life parameters investigated and definitions thereof. Variations of a postulated identical research question can produce surprisingly different study results due to a number of reasons ranging from a different biological background to bias-proned outcome and exposure definitions. Examples of different obesity definitions are obese, overweight, BMI as a continuous outcome, other BMI trajectories, BMI combined with hip-to-waist ratio, BMI associated with metabolic syndrome, etc. comprising a long list of proposed approaches for a major public health issue. Similarly, examples of different exposure definitions include BMI at 2 years, BMI at 1 year, weight gain over the first 2 years, growth velocity, catch-up growth, etc. compromising a long list of exposures that might be tested in association with later overweight and obesity. In fact, postnatal growth itself has a long list of definitions with many studies using smoothing or regression cubic splines in order to model growth—such models are easy to fit but the interpretation of parameters poses challenges—while others have chosen standard parametric approaches to model longitudinal growth—this has the advantage of natural biologic interpretability of

the parameters [3]. Another considerable concern regarding this field is whether reverse causation issues prevail. Are the observed phenotypes related to early growth patterns a proxy of the final adult obesity phenotype—confounded by factors that influence both postnatal weight gain and later adiposity—and any intervention would actually simply suppress the presentation of the underlying disordered pattern of metabolism or modifying growth patterns associated with adult obesity would truly affect the natural history of the disease? Standard regression techniques, which have been used to address the aforementioned hypothesis, have limitations and are often inadequate in addressing these research questions. Reparameterisation of a multiple regression analysis can change the interpretation of the model's results while regression models are usually hindered by collinearity problems. Other techniques such as latent class and path analysis have been proposed to address many of these issues but still are infrequently used in the literature [32].

Overview of the Currently Available Evidence

Many epidemiological studies have examined associations between size at birth, infancy and growth with later measures of obesity in childhood adolescence and adulthood. Here we summarise the evidence from epidemiological studies focusing on studies, which examine association between early size and growth with overweight and obesity in adulthood. We retrieved information from the latest available systematic reviews as well as large (arbitrarily set as of a sample size larger than 1,000 participants) observational studies subsequently published in the field.

Birth Weight and Adult Obesity

Many studies have examined the association between birth weight and later BMI and have shown positive but weak associations between higher birth weight and higher BMI in adulthood [36]. For example, the Health Professionals Follow-Up Study collected self-reported information on birth weight and current height and weight for 51,829 middle-aged men [37]. The OR for being in the highest vs. the lowest age-adjusted BMI quintile was 2.08 (1.73–2.50) for men with a birth weight of over 4.5 kg, and 0.75 (0.66–0.84) for men with a birth weight between 2.5 and 3.1 kg compared to the reference category of 3.2–3.8 kg. A similar analysis was performed in the Nurses Health Study, which had information on 71,100 women aged 30–55 years and 92,940 women aged 25–42 years. Among women aged 30–55 years, the OR of having a BMI in the highest vs. the lowest quintile was 1.62 (95% CI 1.38–1.90) for those with a birth weight >10.0 lb, compared to those with a birth weight of 7.1–8.5 lb [38]. Some studies have also reported a J- or U-shaped relationship between birth weight and obesity but most support a linear relationship [10].

BMI is only a marker of body fat and does not inform on lean and fat mass or fat distribution. It is possible for example that positive associations between birth weight and BMI could result from increases in lean body mass rather than adipose tissue or vice versa [39]. Few studies have addressed this issue and those have reported positive associations between birth weight and subsequent lean body mass, and a negative association with relative adiposity [40]. In addition, other studies have shown inconsistent associations between birth weight and waist circumference [3, 38–40]. These results need to be interpreted with caution as accurate methods of measuring body fat distribution such as DXA scan or whole body MRI scan were not available. Recently, the population based ALSPAC study of 6,000 UK children aged 9–10 years showed positive associations between birth weight and total body lean mass index and fat mass index measured with a DXA scans; however, data on adults is not yet available [41].

Infant Size and Adult Obesity

Many epidemiological studies have examined the association between infant weight and adult obesity addressing the notions for early screening and prevention of obesity in childhood. In a recent systematic review [11], 18 studies which assessed the relationship between infant size and subsequent overweight or obesity were identified. Most studies showed that infants who were obese or overweight had higher risk of being overweight and obese in later life. Only seven of those studies examined the association between infant size and obesity in adulthood again showing consistent positive associations [11]. Despite the observed consistency across study results, a quantitative synthesis of the reported estimates was not possible due the large heterogeneity in the definitions of infant size and subsequent outcomes (obesity). The infant size for example has been defined as BMI at 6 months, as BMI at 1 year, as weight in 1 year, weight in 2 year, weight at 18 months, weight for height and skinfold thickness by various studies. In addition, results need cautious interpretation as risk of bias was high in 5 out of the 18 studies and medium in other 11 studies [11]. The prevailing diversity of exposure definitions in the field arises from lack of in-depth knowledge of the contribution of isolated infant BMI measurements in predicting future obesity [9]. The developmental pattern for BMI differs somewhat from the more-familiar patterns for height and weight; the normal pattern is for BMI to decrease from approximately 2 years of age until 5 or 6 years of age and to increase thereafter. Thus, infancy represents a time period of non-linear decrease and increase in BMI and poses considerable challenges in terms of methodology and interpretation of a postulated prognostic association between isolated infant size estimates and adult obesity. Hence, the available accumulated evidence in the field fails to answer important public health questions and support clinical decisions, the most important being the exact timing for overweight/obesity screening. Subsequent research reflects the difficulty of choosing an isolated infant size estimate and mainly focuses on growth velocity assessment discussed in detail later. The current guidance from the American Academy of Pediatrics recommends a staged approach towards obesity prevention starting the obesity screening at age 2 [41]. Alternatively, in 2010, the USPSTF recommends that clinicians screen children aged 6 years and older for obesity and offer them or refer them to comprehensive, intensive behavioural interventions to promote improvement in weight status [42]. The observed controversy regarding the exact time-point as to when to measure and start screening for obesity led to the alternative approach of involving a more inclusive growth parameter as presented by growth velocity.

Infant Growth and Adult Obesity

Sufficient weight gain is fundamental for a normal growth and development process during childhood. However, it remains unclear if weight gain above the expected or usual weight gain, regardless of its direct impact in crossing the overweight/obesity threshold in infancy, causes additional short-term or long-term benefits or harms. As mentioned in the previous section, several studies of obesity in early childhood have focused on cross-sectional evaluations of obesity prevalence, but, until recently, few have evaluated longitudinal changes in weight status for infants. The association between weight gain in infancy and obesity in childhood, adolescence, and adulthood has recently been widely recognised [2] and a better understanding of weight transitions early in childhood would likely inform future interventional work and policy focused on childhood obesity. In this section, we will discuss the available evidence regarding that research question; associations between catch-up growth patterns and adult obesity in pre-term or small-for-gestational-age born infants as well as in settings with high prevalent malnutrition lie beyond the scope of this section and will not be discussed further. In 2005, Baird et al. [11] published a systematic review of ten studies, which examined the relation

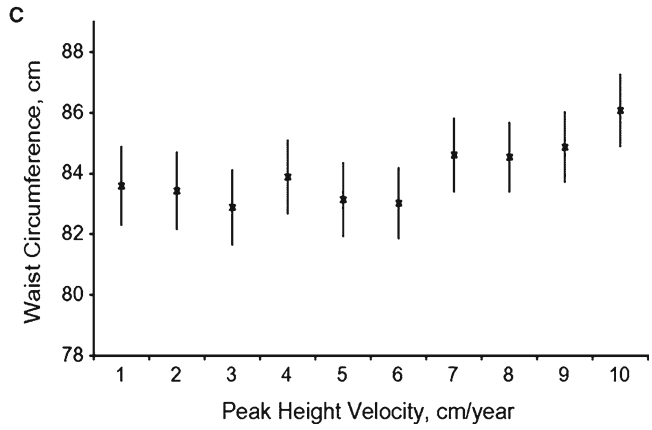

Fig. 28.2 Associations of waist circumference with deciles of peak height velocity in infancy, Northern Finland Birth Cohort 1966 Study [3]

between weight gain in infancy, assessed in various ways, and subsequent obesity, measured as body weight or BMI. Relative risks for subsequent obesity ranged from 1.2 to 5.7 among infants with rapid weight gain. However, in most of the articles reviewed, obesity was measured in childhood or adolescence, information on markers of obesity beyond weight or BMI was scarce, and few studies had repeated measures of growth at different time points. In a following systematic review [43], researchers reported that higher odds ratios were reported from studies with longer duration of the infancy weight gain exposure, younger age when the outcome was measured, and less or no adjustment for potential confounding factors; interestingly, after standardising the observed risk estimates, all studies reported associations of comparable magnitude. Subsequent research in the field, confirms the direction of the postulated association, but lacks again consistency regarding exposure and outcome definitions. In the Caerphilly Growth Study, McCarthy et al. [44] modelled detailed weight changes among 676 boys and girls over the first 5 years of life and reported variable, non-consistent associations between weight gain and adiposity in adulthood that were influenced by the time window of growth and the measure of adiposity used in adulthood. Results from the large Finnish Birth Cohort study, which had detailed and frequent measurements of growth over the first 2 years of life, showed that peak weight velocity (PWV) in infancy was significantly associated with adulthood BMI and waist circumference [3]. A 4-kg/year higher PWV was associated with a 1.87-cm (95% confidence interval: 1.08, 2.65) larger waist circumference in adulthood, after adjustment for potential confounders. In the same study, height velocity was also strongly associated with greater waist circumference independent of adult BMI, despite the high correlation between these two variables (Fig. 28.2). The associations of weight and height growth velocities with waist circumference highlight the fact that early growth might have an effect on later visceral obesity. This is of particular importance, since abdominal adipose tissue, an endocrine organ, secretes adipocytokines and other vasoactive substances and can influence the risk of developing metabolic traits [45].

Future Implications

Tackling obesity remains a public health priority for most developed and developing countries and interventions and policies are greatly needed to prevent and reduce obesity [46]. At the end of the pipeline, the research community is waiting for the emergence of randomised clinical evidence that will eventually validate hypotheses generated and refined through the observational epidemiology framework. These hypotheses are expected to form into community-based interventions that will adequately address the causes of excessive weight gain through different periods of child development, will define the risks and benefits of promoting growth in infancy and will be stringently assessed for causality, generalisability, safety and cost-effectiveness.

Results summarised here support the hypothesis that the first months of life, a period of development that is amenable to intervention, are important in the risk of later overweight and obesity—a major risk factors for cardiovascular disease and other chronic diseases. In future work, investigators need to replicate these results using robust methodologies including and not limited to conceptual standardisation of exposures and outcomes and elucidate potential mechanisms that might explain the reported associations. In addition, these results need to be placed in the context of other findings which have shown beneficial effects of early growth on later development of diabetes and other outcomes, including brain development [47]. Little is known about associations between early growth and other outcomes such as depression and cancer, which are other main causes of morbidity and mortality in adulthood [47, 48]. A better understanding of mechanisms throughout the life course that contribute to obesity, cardiovascular risk, and other health outcomes is important and would have important implications for prevention of chronic disease in adulthood [3].

References

1. World Health Organization. Obesity and overweight (WHO information sheet). Geneva, Switzerland: World Health Organization; 2003. http://www.who.int/dietphysicalactivity/publications/facts/obesity/en/. Accessed 10 June 2009.
2. Gillman MW. The first months of life: a critical period for development of obesity. Am J Clin Nutr. 2008;87:1587–9.
3. Tzoulaki I, Sovio U, Pillas D, Hartikainen AL, Pouta A, Laitinen J, et al. Relation of immediate postnatal growth with obesity and related metabolic risk factors in adulthood: the northern Finland birth and related metabolic risk factors in adulthood: the northern Finland birth cohort 1966 study. Am J Epidemiol. 2010;171:989–98.
4. Barker DJ, Osmond C, Forsén TJ, et al. Trajectories of growth among children who have coronary events as adults. N Engl J Med. 2005;353(17):1802–9.
5. Eriksson JG, Forsén T, Tuomilehto J, et al. Early growth and coronary heart disease in later life: longitudinal study. BMJ. 2001;322:949–53.
6. Harder T, Rodekamp E, Schellong K, et al. Birth weight and subsequent risk of type 2 diabetes: a meta-analysis. Am J Epidemiol. 2007;165:849–57.
7. Laurén L, Järvelin MR, Elliott P, et al. Relationship between birthweight and blood lipid concentrations in later life: evidence from the existing literature. Int J Epidemiol. 2003;32:862–76.
8. Srinivasan M, Patel MS. Metabolic programming in the immediate postnatal period. Trends Endocrinol Metab. 2008;19:146–52.
9. Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life—a systematic review. Obes Rev. 2005;6:143–54.
10. Rogers I, EURO-BLCS Study Group. The influence of birthweight and intrauterine environment on adiposity and fat distribution in later life. Int J Obes Relat Metab Disord. 2003;27:755–77.
11. Baird J, Fisher D, Lucas P, et al. Being big or growing fast: systematic review of size and growth in infancy and later obesity. BMJ. 2005;331(7522):929.
12. Bergvall N, Cnattingius S. Familial (shared environmental and genetic) factors and the foetal origins of cardiovascular diseases and type 2 diabetes: a review of the literature. J Intern Med. 2008;264:205–23.
13. Barker DJP. Fetal and infant origins of adult disease. London: BMJ Publishing; 1992.
14. Gillman MW. Developmental origins of health and disease. N Engl J Med. 2005;353:1848–50.
15. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002;31:285–93.
16. Hattersley AT, Tooke JE. The fetal insulin hypothesis: an alternative explanation of the association of low birthweight with diabetes and vascular disease. Lancet. 1999;353:1789–92.
17. Bateson P, Barker D, Clutton-Brock T, et al. Developmental plasticity and human health. Nature. 2004;430:419–21.
18. Jaddoe VW, Witteman JC. Hypotheses on the fetal origins of adult diseases: contributions of epidemiological studies. Eur J Epidemiol. 2006;21:91–102.
19. Silveira PP, Portella AK, Goldani MZ, et al. Developmental origins of health and disease (DOHaD). J Pediatr (Rio J). 2007;83:494–504.
20. Hocher B. Fetal programming of cardiovascular diseases in later life—mechanisms beyond maternal undernutrition. J Physiol. 2007;579:287–8.
21. Seckl JR. Prenatal glucocorticoids and long-term programming. Eur J Endocrinol. 2004;151 Suppl 3:U49–62.

22. Cottrell EC, Seckl JR. Prenatal stress, glucocorticoids and the programming of adult disease. Front Behav Neurosci. 2009;3:19.
23. Wyrwoll CS, Seckl JR, Holmes MC. Altered placental function of 11beta-hydroxysteroid dehydrogenase 2 knockout mice. Endocrinology. 2009;150:1287–93.
24. Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. J Hypertens. 2000;18:815–31.
25. Ozanne SE, Constancia M. Mechanisms of disease: the developmental origins of disease and the role of the epigenotype. Nat Clin Pract Endocrinol Metab. 2007;3:539–46.
26. Gluckman PD, Hanson MA, Buklijas T, et al. Epigenetic mechanisms that underpin metabolic and cardiovascular diseases. Nat Rev Endocrinol. 2009;5:401–8.
27. Criscuolo F, Monaghan P, Nasir L, et al. Early nutrition and phenotypic development: 'catch-up' growth leads to elevated metabolic rate in adulthood. Proc Biol Sci. 2008;275:1565–70.
28. Singhal A, Lucas A. Early origins of cardiovascular disease: is there a unifying hypothesis? Lancet. 2004;363:1642–5.
29. Langley-Evans SC. Developmental programming of health and disease. Proc Nutr Soc. 2007;65:97–105.
30. McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. Physiol Rev. 2005;85:571–633.
31. Bieswal F, Ahn MT, Reusens B, et al. The importance of catch-up growth after early malnutrition for the programming of obesity in male rat. Obesity (Silver Spring). 2006;14(8):1330–43.
32. Gamborg M, Jensen GB, Sørensen TI, Andersen PK. Dynamic path analysis in life-course epidemiology. Am J Epidemiol. 2011;173:1131–9.
33. Freathy RM, Bennett AJ, Ring SM, et al. Type 2 diabetes risk alleles are associated with reduced size at birth. Diabetes. 2009;58:1428–33.
34. Freathy RM, Weedon MN, Bennett A, et al. Type 2 diabetes TCF7L2 risk genotypes alter birth weight: a study of 24,053 individuals. Am J Hum Genet. 2007;80:1150–61.
35. Sovio U, Mook-Kanamori DO, Warrington NM, et al. Association between common variation at the FTO locus and changes in body mass index from infancy to late childhood: the complex nature of genetic association through growth and development. PLoS Genet. 2011;7(2):e1001307.
36. Yu ZB, Han SP, Zhu GZ, Zhu C, Wang XJ, Cao XG, et al. Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. Obes Rev. 2011;12:525–42.
37. Curhan GC, Chertow GM, Willett WC, Spiegelman D, Colditz GA, Manson JE, et al. Birth weight and adult hypertension and obesity in women. Circulation. 1996;94(6):1310–5.
38. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Ascherio AL, Stampfer MJ. Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. Circulation. 1996;94:3246–50.
39. Fall CH. Evidence for the intra-uterine programming of adiposity in later life. Ann Hum Biol. 2011;38:410–28.
40. Byberg L, McKeigue PM, Zethelius B, Lithell HO. Birth weight and the insulin resistance syndrome: association of low birth weight with truncal obesity and raised plasminogen activator inhibitor-1 but not with abdominal obesity or plasma lipid disturbances. Diabetologia. 2000;43:54–60.
41. Gale CR, Martyn CN, Kellingray S, Eastell R, Cooper C. Intrauterine programming of adult body composition. J Clin Endocrinol Metab. 2001;86:267–72.
42. Barlow SE, Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics. 2007;120 Suppl 4:S164–92.
43. Ong KK, Loos RJ. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions. Acta Paediatr. 2006;95:904–8.
44. McCarthy A, Hughes R, Tilling K, et al. Birth weight; postnatal, infant, and childhood growth; and obesity in young adulthood: evidence from the Barry Caerphilly Growth Study. Am J Clin Nutr. 2007;86:907–13.
45. Fox CS, Massaro JM, Hoffmann U, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation. 2007;116:39–48.
46. Khan LK, Sobush K, Keener D, Goodman K, Lowry A, Kakietek J, et al. Centers for Disease Control and Prevention. Recommended community strategies and measurements to prevent obesity in the United States. MMWR Recomm Rep. 2009;58:1–26.
47. Fisher D, Baird J, Payne L, et al. Are infant size and growth related to burden of disease in adulthood? A systematic review of literature. Int J Epidemiol. 2006;5:1196–210.
48. Gluckman PD, Hanson MA, Cooper C, et al. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008;359:61–73.

Chapter 29
Maternal Behavior and Infant Weight

John Worobey

Key Points

- Child obesity rates are at an epidemic level, with rates during infancy also alarming.
- Numerous factors, including maternal feeding style, are thought to be related to infant overweight.
- Mothers whose infants are overweight appear to restrict while mothers whose infants are underweight are likely to pressure.
- A mother can overfeed by virtue of failing to heed her infant's satiety signals, with a resultant heavier infant.
- Clinicians can help guide mothers to better read their infants' hunger and satiety cues.

Keywords Maternal feeding style • Infant weight gain • Maternal control • Restrictive feeding • Pressure to feed

Introduction

When Charney et al. [1] posed the question, "Do chubby infants become obese adults?" in the *New England Journal of Medicine* in 1976, few would have anticipated the obesity epidemic we currently face, or the urgent need to examine all possible factors that may be contributing to this serious health problem. With the sobering realization that our youngest are not immune to this epidemic, as alarming rates of overweight and obesity are even apparent in early childhood [2] scientists across a wide array of disciplines are desperately seeking answers and are increasingly looking at the earliest correlates of obesity with an eye toward prediction and prevention. To this end, increasing attention is being paid to weight and weight gain in infancy. While numerous explanations have emerged which serve to identify the risk factors that promote early excess infant weight gain, for example, low birth weight, maternal overweight, or not breastfeeding [3], an intriguing line of recent research has focused on the role of the caregiver (hereafter, mother) from a behavioral perspective. That is, do the behaviors that a mother exhibits in the context of feeding have any bearing on how much her infant ingests, and ultimately, on her infant's weight trajectory?

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A number of recent reviews have concluded that sustained breastfeeding serves as a deterrent to later obesity [4–6], although the mechanism by which it does so is not fully understood [7]. As it has long been established that formula-fed infants begin to surpass breast-fed infants in terms of weight gain by 2–3 months [8], one hypothesis favors the unique properties of human milk. Despite the best efforts by scientists to imitate human breast milk in reconstituting and fortifying cow's milk to manufacture infant formula, the composition of breast milk and formulas remain biochemically different. Indeed, recent work suggests that certain hormones such as leptin or ghrelin, present in breast milk but not in formula, may be partially responsible for the infant's self-regulation of appetite [9].

Alternately, rapid weight gain may be due in part to maternal overfeeding. When one considers that the human infant is totally dependent on the mother to obtain nourishment, a viable complementary explanation is that a mother's aggressive approach to feeding may led to overfeeding and subsequently, the infant's ability to self-regulate being undermined with the consequence of excess weight gain. Conversely, a passive approach to feeding might lead to underfeeding and subsequently to underweight. The aim of this chapter is to review the available studies on maternal behavior in the feeding context, to address the question as to whether maternal feeding practices exert a meaningful influence on infant weight.

Feeding Patterns and Scheduling

The formal study of maternal feeding styles by scientists (Freudian theory notwithstanding) can trace its roots to the seminal volume by Brody [10], who over a half century ago categorized mothering into four patterns, based on maternal sensitivity, consistency, and frequency of behaviors. Her rich descriptions of 32 mostly breastfeeding mothers, with infants ranging from 4 to 28 weeks, are a worthwhile read even today for anyone who aspires to study mother-infant interaction. For the purposes of infant weight as an outcome, her description of the "C mothers" is most informative:

> The mothers of group C were conspicuous for their lack of spontaneity and their intentions to be efficient above all else. Physically and socially they were detached from their infants. Some reduced their attention to the carrying out of a minimum of essential details of infant care, and showed a low degree of interest in any activity with the infant of a non-physical nature ([10], p. 266).

Nevertheless, by the end of her observations, the C infants exhibited the highest percentage of weight gain, at 107.32 %. On an earlier page Brody states "that the C mothers, outside of Feeding, did little with their infants" (p. 261), a summation that may be unduly critical, since during feeding those mothers were highest in speaking to their infants, and never lower than second in moving, touching or offering their infants objects, relative to the A, B and D mothers. In any case, this treatise serves as one of the earliest reports on how less sensitive mothering may be associated with infant weight gain.

Concurrent with their early work on mother-infant interactions, Ainsworth and Bell [11] conducted a comprehensive study that targeted feeding patterns. While infant attachment behaviors later displayed at 12-months were a primary outcome of interest, the investigators made detailed enough notations to link maternal feeding behavior to infant weight gain. Despite a sample of only 26 mothers who were mostly bottle-feeders, the authors delineated nine feeding patterns over the first 12-weeks postpartum: four patterns were designated as feeding on demand, four were designated as feeding on a schedule, and one was designated as arbitrary. While breast vs. bottle feeding provides an obvious dichotomy in the study of maternal feeding style, with this investigation Ainsworth and Bell contributed "demand" vs. "schedule" feeding as a variable of interest.

The Ainsworth and Bell [11] sample revealed five infants, all bottle-fed, as being overweight at 3-months. Two of the overweight infants had mothers who were described as Scheduled feeding (pattern IV), with their intent labeled as overfeeding to gratify baby. But both of the infants whose mothers were described as Demand feeding (pattern III), were similarly recorded as being overweight,

with their intent also labeled as overfeeding to gratify baby. The mother of the fifth overweight infant was categorized as Pseudo-Demand (pattern VII), that is, overfeeding to make her baby sleep long. Interestingly, of the four infants who were observed to be underfed, two were underweight, while a fifth infant fed normally was also underweight. Three of the four underweight infants had mothers characterized as Pseudo-Demand (pattern VI) but in this pattern, because mother was judged as impatient.

Despite the landmark nature of these two publications, until hints of an imminent obesity crisis began to surface, essentially no research on maternal behavior and infant weight outcomes was conducted for some 30-odd years. Granted, an occasional report would appear, notably Klesges et al. [12] exemplary work in observing families at mealtimes, where connections could be made between parental encouraging of toddlers to eat and their higher weight. But such studies used cross-sectional approaches, and the few infants included had long been weaned to solid foods. For such reasons, a study by Casiday et al. [13] is noteworthy because of its recency, magnitude, and focus on feeding patterns in the first week postpartum. The investigators compared breast-, bottle- and mixed-fed infants (Ns of 172, 278 and 52, respectively), and found no associations between bottle- or mixed-feeds and weight measures at 6 weeks. For breast-fed infants, a lower feed-to-feed ratio, that is, more frequent feedings, was associated with higher weight gain. Inasmuch as the breast-fed infants were lighter in weight than the infants of the other groups, frequency of feeding in this case was not a harbinger of obesity risk, but likely desirable for the breast-fed infants.

In sum, these varied results over separate decades do provide a basis for the consideration of early feeding patterns as a causal mechanism for weight outcomes. While some evidence suggests that overfeeding by bottle-feeding mothers seemed to lead to overweight, the finding that feeding frequency could even influence breast-fed infants growth rates underscores the role of maternal behavior.

Although the issue of demand vs. schedule feeding has garnered some popular airplay in the "advice to parents" realm, with rather impassioned arguments for and surprisingly against demand feeding [14, 15], remarkably little empirical work has been conducted that has examined the impact of such patterns on infant growth. In a study with 29 preterm infants, Saunders, Friedman and Stramoski [16] reported that weight gains were similar across feeding groups, whether demand- or schedule-fed. In a study by Baughcum et al. [17], ostensibly conducted to develop and validate their Infant Feeding Practices Questionnaire (IFPQ) for assessing maternal feeding practices and beliefs, no associations were found between feeding on demand or on a schedule, and this with a sample of 453 infants. More recently, Saxon et al. [18] conducted a retrospective examination of infant feeding practices over the first year with the expressed intent of comparing demand to schedule feeding. Their data on 21 demand-vs. 27 schedule-fed infants suggested no pervasive differential effect of feeding type on infant growth from birth to 6 months. Coupled with the early Ainsworth and Bell [11] results, it would appear then that feeding on demand vs. on a schedule makes little if any difference in infant weight outcomes.

Maternal Feeding Style Versus Feeding Practices

The aforementioned study by Baughcum et al. [17] that dismissed feeding schedule as having any bearing on infant weight, did report that mothers expressed greater concern about their infants overeating if their infants were overweight. However, no associations were found between infant overweight status and maternal awareness of infant hunger/fullness cues or using food to calm the infant, or toddler overweight and use of food to calm toddler fussing, pushing the toddler to eat more, or letting the toddler control the feeding interaction. Given these non-results, the authors concluded that there was no particular maternal "feeding style" that is associated with early overweight. In spite of

this assessment, a line of research has picked up on the notion of feeding style, conceiving it as a derivative of overall parenting style.

The roots of research on parenting style lie in the domain of developmental psychology, owing to Schaefer's [19] initial formulation of two primary dimensions of parental behavior (warmth-hostility and autonomy-control), and Baumrind's [20] later assignment of labels to certain of the possible combinations (namely authoritative, authoritarian, and permissive). Drawing on this and related research, Maccoby and Martin [21] re-conceptualized parenting style along the two dimensions of parental responsiveness (aka warmth or supportiveness) and demandingness (aka behavioral control), to classify the pairings of their high and low exhibition as authoritative, authoritarian, permissive, and uninvolved. For example, an authoritative parenting style would connote high responsiveness and high demandingness, while an uninvolved parent would be low on both dimensions. Scores of studies using this typology attest to the authoritative style as being associated with the most positive child outcomes [21, 22].

In what may be hailed as an overdue meeting of the child psychology and nutritional science fields, Hughes et al. [23] have applied the parenting style approach to the study of child obesity, narrowing the former to how parenting style may align with child feeding styles. For example, an indulgent feeding style would be characterized as high in responsiveness (e.g., allowing the child to choose appropriate foods) and low in demandingness (e.g., letting the child not eat his string beans). Although some evidence suggests that this typology has been fruitful with preschool-age children in finding associations between feeding style and sources of energy intake as well as overweight status [23, 24], the utility of the feeding style approach has not been tested with mothers of infants. That is, some work has shown that mothers of infants can be categorized in this manner, for example, indulgent or laissez-faire [25], but no research to date has explored whether or not these blended feeding styles relate to infant weight or excess weight gain.

Ventura and Birch [26] make an important distinction between parental feeding *styles* and parental feeding *practices*. In their view, a feeding style (as a specific case of parenting style) implies that a mother possesses an almost trait-like style that describes how she would interact with her children across all feeding situations. Thus, an authoritarian mother would be expected to be high in demandingness and low in responsiveness when feeding any of her children, irrespective of setting, the child's gender, or one might add, the child's weight status. In contrast, a feeding practice would be context-related, that is, a specific behavior employed to control when, what, and how much her child will eat [26]. From this perspective, feeding practices include behaviors such as pressuring a child to eat, restricting a child from eating, monitoring foods the child eats, using food as a reward, modeling what foods to eat, or using food to pacify. If not obvious, such behaviors infer the exertion of control over the feeding situation, and therefore echo the autonomy-control continuum of the parenting styles framework. However, the distinction is one of behavior aimed at control rather than a controlling personality.

Maternal Control and Infant Weight

In fairness, the element of control is crucial to the demandingness dimension, witness the feeding style reports that address controlling behaviors such as food restriction [23, 25]. While the practices listed above would seem to have greater saliency for preschool-age children than for infants, however (e.g., using food as a reward), the issue of control provides a common denominator. Consider, for example, the relevance of control in the act of breastfeeding. Numerous investigators have proposed that breastfeeding mothers are relatively less able to monitor the quantity of milk that their infants ingest, and thereby relinquish more control to the infants [27–29]. The bottle-feeding mother, in contrast, can exert greater control of when, where and how much her infant may be fed, and behaviors like monitoring, restricting, and pressuring are more likely to be used as the mother begins to attend to her infant's growth rate. Irrespective of breast or bottle-feeding, in recent years nearly a dozen studies

have appeared that have been directed toward linking feeding practices such as these to infant weight gain and overweight.

Fisher et al. [30] may be credited with the first attempt to tie maternal control of feeding to infant weight, along with the logical precursor of early weight gain, namely energy intake. Of particular interest to these authors were the possible differences between their 11 bottle-feeding and 44 breastfeeding dyads. Using a set of self-report items aimed at measuring maternal control of feeding at 12–13 months, along with diet records for the infants reaching toddlerhood at 18-months, the investigators found that lower infant weights were associated with lower maternal control in feeding, and that breastfeeding through the first year predicted maternal control, with women still breastfeeding at 12–13 months tending to report lower control. But unexpectedly, lower maternal control at 12–13 months was associated with higher toddler energy intake at 18 months. In turn, higher energy intake was shown for larger toddlers, that is, toddlers who were taller and leaner, but not heavier. The authors interpreted their maternal control–heavier toddler association as suggesting that infant weight status may have been considered by the mother in determining how much she should exert control in feeding her toddler.

Concerned about weight faltering and failure to thrive, Wright et al. [31] surveyed mothers at 6-weeks and 4-, 8- and 12-months on their infants' feeding behavior. While most of their questions focused on infant feeding problems (e.g., oromotor dysfunction, avoidant eating behavior), the authors included a subscale labeled "maternal response to food refusal." With items that ask if the mother re-offers food or makes the child eat if part of the meal is not finished, this form of behavior would assuredly qualify as control through pressuring. For their sample of 537 infants at 12 months, a higher level of such pressuring predicted lower weight gain. Although mothers may have been responding to their infant's tendency to undereat, or encouraging their thinner infants to eat more, the authors caution that maternal pressure to eat may have the unintended effect of causing food avoidance.

Although their preschool-age sample lies outside the age-range for infancy and toddlerhood, Burdette et al. [32] asked mothers of 3-years-old to recall their feeding practices during their infants' first year of life using the IFPQ, then re-weighed and measured the children when they reached age 5. Mothers who reported having exerted higher control over infant feeding, albeit 4 years earlier, tend to have children with lower fat mass at 5 years ($p<0.07$). Mothers of overweight 5-years-old also reported being more concerned about infant overeating when asked at age 3. However, no associations were found between child weight and awareness of satiety cues, using food to calm fussiness, feeding the infant as first response if fussing, feeding on a schedule, or breastfeeding.

Farrow and Blissett [33], in a departure from the questionnaire approach, observed 69 mothers as they fed their infants solids at 6 months, and obtained weight measures of the infants at birth, 6 and 12 months. The videotaped feeding interactions were rated for maternal use of control during feeding, with a highly controlling caregiver continuously offering, forcing, or positioning the infant to eat. In cases where maternal control at 6 months was high, infant growth from 6 to 12 months followed a pace similar to that shown from birth to 6 months. However, where maternal control was low, the infant growth pattern reflected a compensatory form of self-regulation. That is, infants with rapid early weight gain slowed down from 6 to 12 months while those with slow early weight gain accelerated in their subsequent weight gain. Breastfeeding was not associated with infant growth from 6 to 12 months. These results offer clear evidence that maternal control can exert an influence on infant weight outcomes, but at the same time indicate the need to consider the infant's predicted growth trajectory.

Food Restriction and Pressure to Eat

While the above results do not suggest a convergent pattern for maternal control and its association with infant weight gain, other factors that also cloud interpretation are the varied ages of the targeted infants, as well as the nature of the instruments used. For example, three of the four studies just

reviewed used different sets of questions to measure maternal control [30–32] while the fourth study relied on ratings of observations [33]. As a case in point, the instrument employed by Fisher and colleagues, until then used only with children aged 3–5 years [34] included questions that tapped food restriction, pressuring, and use of food as a reward, combining them into a control score that confounded these three practices. Shortly after their study appeared, however, the instrument was published in a validated form as the Child Feeding Questionnaire (CFQ) that differentiates between restriction, pressure to eat, and monitoring [35]. For example, one *restriction* item is "I have to be sure my child does not eat too many sweets," while a *pressure to eat* item is "I have to be especially careful to make sure my child eats enough." Although the items follow a "child feeding" nomenclature, the CFQ has increasingly been used with mothers of infants, as some investigators have deemed the items as suitable once infants have been introduced to complementary foods.

For example, Taveras et al. [36], who also sought to explore the association between breastfeeding and maternal control, used items from the CFQ to measure restriction and pressuring to eat. Their large multiethnic sample of mothers ($N = 1{,}160$) was queried at 1 year as to type of infant feeding, and if breastfeeding, its duration. Mothers who breastfed were less restrictive than bottle-feeding mothers, and the longer they breastfed, the less restrictive they were at 12 months. Breastfeeding did not predict pressuring, nor did infant birth weight or weight-for-length at 6 months relate to breastfeeding duration or maternal control. Curiously, the authors did not include infant weight-for-length at 12 months in their report.

In a pair of reports, Blissett and Farrow tracked infant weight at birth to 12- and 24-months for 62 infants, and had mothers respond to the CFQ at 12- and 24-months [37, 38]. Maternal restriction, pressure and monitoring were correlated with standardized infant weights at three ages, with significant associations for only the following: higher birth weight was associated with less pressure to eat at 12 months and higher infant weight at 12 months with more restriction at 12 months [37]. Higher maternal pressure at 12 months predicted lower toddler weight at 24 months, yet at the same time, higher maternal restriction at 12 months also predicted lower toddler weight at 24 months [38]. Although a longer duration of breastfeeding was associated with lower scores for maternal control (i.e., less pressure and restriction), monitoring was higher for these mothers; yet breastfeeding was not associated with infant or toddler weight. While the authors concluded that as early as 1 year of age, controlling feeding practices may impact upon toddler weight, they raised the possibility that the mothers may have used pressure to eat in response to the perception of or actual infant underweight [38].

A recent study that also employed the CFQ to measure maternal control of feeding has bearing on this issue. Using an online questionnaire methodology, Brown and Lee [39] surveyed a relatively large sample of mothers, with maternal estimates of weight and length provided for 628 infants of age 6–12 months. Mothers completed the CFQ along with a questionnaire that asked about their own eating behaviors. Infant birth weight and maternal feeding practices were not associated, but a heavier current infant weight was significantly associated with higher maternal restriction and lower pressure to eat. More telling, perhaps, was the finding that independent of actual infant weight, mothers who perceived their infants as heavier than average expressed more concern about their infants' weight, monitored their infants' intake more, restricted their infants' intake more, and pressured them to eat less. In addition, mothers who had their own weight concerns (e.g., higher BMI, higher dietary restraint), scored higher on restrictive feeding and concern for their infants' weight, again independent of actual infant weight. These results indicate that maternal concerns for and perceptions of infant weight may be intertwined, with mothers' feeding practices moving toward restriction or pressure, respectively, if they viewed their infant as being overweight or underweight. As must be acknowledged with any correlational analysis, however, that infants who were restricted more were heavier and infants pressured more were lighter indicates that maternal controlling practices may instead have been a response to the infants' actual weight.

This hypothesis is supported by the results of Rifas-Shiman et al. [40] who reduced the CFQ restriction subscale into a single item, that is "I have to be careful not to feed my child too much," and

scored it in an Agree–Disagree manner. As part of a prospective cohort study of 628 mother–infant pairs, these investigators found that maternal restriction at both 6- and 12-months was associated with higher child BMI *z*-scores at age 3 before, *but not after*, adjusting for weight-for-length scores at the earlier ages. Maternal restriction was not associated with infant birth weight, but it did predict duration of breastfeeding, as non-restricting mothers' breast fed their infants for well over 2 months longer than restricting mothers. The authors concluded that mothers may be restricting the food intake of infants who are already overweight.

Responsive and Sensitive Feeding

From the evidence above, a mother's effort to control feeding may be construed as reflecting an intentional set of maternal behaviors aimed at regulating her infant's food intake—whether proactively to avoid her infant becoming over- or underweight, or reactively in response to her infant's actually being over- or underweight. There is another dimension of feeding behavior, however, that may be less premeditated and more dependent on a mother's skill set in reading her infant's hunger and satiety cues. To borrow again from developmental psychology, the area of infant attachment has isolated two aspects of parenting that are paramount in promoting a secure infant-mother relationship [41]. *Sensitivity* refers to how well the mother reads her infant's cues, while *responsiveness* refers to how promptly she reacts to her infant's signals. While sensitivity and responsiveness serve as the foundation for establishing a secure attachment, which in turn is predictive of a variety of positive child outcomes [42], the role of these caregiver characteristics has only recently been considered with respect to the context of feeding [43]. This is somewhat ironic, given the early work by Brody [10] and Ainsworth [11] that stands as the first instances of scrutinizing the dynamics of maternal feeding during infancy. Nonetheless, a few recent studies are illustrative of the role that these behavioral assets may play in affecting infant weight.

Using a cross-sectional design, Thompson et al. [44] studied 150 mother-infant pairs, with 30 dyads at each of the ages 3-, 6-, 9-, 12- and 18-months. In validating the questionnaire which they developed, the investigators assessed what they termed a responsive feeding style, with their final model including a scale for responsiveness to hunger and satiety cues. Initiating a feeding when her infant is deemed to be hungry and terminating the feed when the infant repeatedly turns away or falls asleep would represent responsiveness. Both their exploratory and multiple regression analyses of the differences in infants' weights associated with feeding styles revealed that the weight-for-length *z*-scores were lower in infants whose mother had higher scores for responsiveness to satiety cues.

In contrast, Worobey et al. [45] employed a longitudinal approach to track growth in formula-fed infants from birth through 3-, 6-, and 12-months. At 3- and 6-months they observed a feeding bout at the family's home, using the Feeding Scale of the NCAST system, a checklist that allows for the live recording of mother and infant contingent behaviors during feeding [46]. Of special interest was the subscale of sensitivity to cues, which credits the mother for appropriate handling and verbalizing to her baby, as well as pausing, pacing, and terminating the feed as signaled by the infant. A higher sensitivity score therefore indicates the mother's ability to read her infant's satiety cues. None of the perinatal measures predicted growth from birth to 3-months, nor did 3-month measures to growth from 3 to 6 months. However, maternal sensitivity to infant cues at 6 months was inversely predictive of infant weight gain from 6 to 12 months, with more reported feeds/day positively related. In other words, mothers who were less adept at reading their infants' satiety signals, and who may be assumed to overfeed, had infants who subsequently gained greater amounts of weight. As 40 % of the sample infants were at or above the 85th percentile of weight for length at 12 months (up from 30 % at 6 months), the cumulative effect of overfeeding should not be minimized.

Conclusion

Since the advent of the current obesity crisis, researchers from a broad array of disciplines have sought answers to explain why this epidemic has occurred, and more important, how it can be slowed or reversed. As it is painfully evident that even children are exhibiting obesity in alarming numbers [2], increasing efforts have been made to identify the earliest factors that contribute to childhood overweight. Apart from research in genetics, nutrition, or physical activity, an appreciable body of research has emerged that has examined aspects of parenting, specifically parental feeding strategies, as a correlated if not causal factor in predicting excess child weight gain. A 2004 literature review of 22 studies with child samples predominantly under age 6-years identified numerous inconsistencies across methods and results, but concluded that parental feeding restriction was generally associated with increased child body weight, as well as energy intake [47]. A subsequent review of 67 studies in 2008, again predominantly of young children, echoed the relevance of restriction but provided evidence that heavier children elicit restrictive feeding practices [26]. As for pressuring to eat, the same review concluded that the use of pressure is elicited by parental concerns about child underweight; yet pressuring does not appear to produce the desired effect of children consuming more food. However, feeding an infant is not the same as offering a child an array of foods, and with infant growth remarkably rapid, similarly labeled maternal feeding practices may take a different form.

To be sure, the study of maternal feeding practices in infancy has a short history, hence only a handful of reports are available to date. Despite a limited number, however, their results provide more than their share of inconsistencies. At a minimum, different feeding questionnaires were used by different investigators. Some mothers were enrolled from the time of their infants' birth [38], while others were asked to recall their infant feeding strategies when their children were age 3 years [32]. Greater maternal control in feeding was associated with higher infant weight in one investigation [30], lower weight gain in another [31], and unrelated in a third [36]. Likewise, higher birth weight explained less pressuring at 12 months in one study [37], but predicted nothing in another [39]. Feeding schedule may not matter, but breastfeeding may [32, 38].

So what can be made of these discrepant results? While feeding an infant may foreshadow feeding a child to some degree, the developmental differences between a 6-month-old and 6-year-old are phenomenal. Practices like restriction and pressuring to eat may prove to be, as has been suggested for children, driven by the infant's weight status. That is, mothers whose infants are overweight may restrict, although mothers whose infants are underweight are far likelier to pressure. After all, the appearance of a fat baby still remains as a marker of good mothering in the eyes of some [48], even in an era when child obesity is feared, so maternal attempts to pressure or overfeed are important to investigate. Unlike pressuring a child to eat where food refusal may be part of the dynamic, however, it does seem the case that in infancy, a mother can overfeed by virtue of failing to heed her infant's satiety signals. Whether done "to gratify baby" [11] or due to lower sensitivity [45], overfeeding may be practiced by some mothers with a resultant heavier infant. While less a risk for breastfeeding mothers, pumped milk that is later fed to supplement an infant's daily intake can still lead to overfeeding.

While the implication for clinicians may be to help mothers understand the associated risks of infant overweight, and guide them to better read their infants' hunger and satiety cues [49], a directive for researchers follows from the intriguing results of Blissett and Farrow [37, 38]. Recall they observed that high maternal control served to keep infants growing on the pace they displayed in their first few months, whether under- or overweight, while low control appeared to allow the infant to self-regulate to a healthier weight. Future work would do well to record growth and feeding patterns from birth onward, so as to better gauge the role of maternal feeding style in tandem with the infant's growth trajectory.

References

1. Charney E, Goodman HC, McBride M, Lyon B, Pratt R. Childhood antecedents of adult obesity: do chubby infants become obese adults? N Engl J Med. 1976;295(1):6–9.
2. Centers for Disease Control and Prevention. Obesity rates among low-income preschool children. http://www.cdc.gov/obesity/childhood/data.html. Accessed 30 July 2011.
3. Worobey J. Risk factors for obesity in early human development. In: Fitzgerald HE, Mousouli V, editors. Obesity in childhood and adolescence: Understanding development and prevention, vol. 2. Westport, CT: Praeger; 2008. p. 3–23.
4. Arenz S, Ruckerl R, Koletzko B, von Kries R. Breastfeeding and childhood obesity: a systematic review. Int J Obes. 2004;28:1247–56.
5. Harder T, Bergmann R, Kallischnigg G, Plagemann A. Duration of breastfeeding and risk of overweight: a meta-analysis. Am J Epidemiol. 2005;162:397–407.
6. Owen CG, Martin RM, Whincup PH, Smith GD, Cok DG. Effect of infant feeding on risk of obesity across the life course: a quantitative review of published evidence. J Pediatr. 2005;115:1367–77.
7. Bartok CJ, Ventura AK. Mechanisms underlying the association between breastfeeding and obesity. Int J Pediatr Obes. 2009;4(4):196–204.
8. Dewey KG, Heinig MJ, Nommsen LA, Peerson JM, Lönnerdal B. Breast-fed infants are leaner than formula-fed infants at 1-year of age: the DARLING Study. Am J Clin Nutr. 1993;57:140–5.
9. Dundar NO, Anal O, Dundar B. Longitudinal investigation of relationship between breast milk leptin levels and growth in breast fed infants. J Pediatr Endocrinol Metab. 2005;18:181–7.
10. Brody S. Patterns of mothering. New York: International Universities Press; 1956.
11. Ainsworth MDS, Bell SM. Some contemporary patterns of mother-infant interaction in the feeding situation. In: Ambrose A, editor. Stimulation in early infancy. New York: Academic; 1969. p. 133–63.
12. Klesges RC, Coates TJ, Brown G, Sturgeon-Tillisch J, Moldenhauer-Klesges LM, Holzer B, et al. Parental influences on children's eating behavior and relative weight. J Appl Behav Anal. 1983;16:371–8.
13. Casiday RE, Wright CM, Panter-Brick C, Parkinson KN. Do early feeding patterns relate to breast-feeding continuation and weight gain? Data from a longitudinal cohort study. Eur J Clin Nutr. 2004;58:1290–6.
14. Ezzo G, Ezzo EM. Preparation for parenting: bringing God's order to your baby's day and restful sleep to your baby's night. Simi Valley, CA: Growing Families International Press; 1995.
15. Sears W, Sears M. The attachment parenting book: a commonsense approach to understanding and nurturing your baby. New York: Little, Brown & Company; 2001.
16. Saunders RB, Friedman CB, Stramoski PR. Feeding preterm infants: schedule or demand? J Obstet Gynecol Nurs. 1991;20(3):212–8.
17. Baughcum AE, Powers SW, Johnson SB, Chamberlin LA, Deks CM, Jain A, et al. Maternal feeding practices and beliefs and their relationships to overweight in early childhood. J Dev Behav Pediatr. 2001;22(6):391–408.
18. Saxon TF, Gollapolli A, Mitchell MW, Stanko S. Demand feeding or schedule feeding: infant growth form birth to 6 months. J Reprod Infant Psychol. 2001;20(2):89–99.
19. Schaefer E. A circumplex model for maternal behavior. J Abnorm Soc Psychol. 1959;59:226–35.
20. Baumrind D. Current patterns of parental authority. Dev Psychol Monogr. 1971;4:1–103.
21. Maccoby EE, Martin JA. Socialization in the context of the family. In: Mussen PH, editor, Hetherington EM, volume editor. Handbook of child psychology: socialization, personality and social development, vol. 4. New York: Wiley; 1983. p. 1–101.
22. Darling N, Steinberg L. Parenting style as context: an integrative model. Psychol Bull. 1993;113(3):487–96.
23. Hughes SO, Power TG, Fisher JO, Mueller S, Nicklas TA. Revisiting a neglected construct: parenting styles in a child feeding context. Appetite. 2005;44:83–92.
24. Patrick H, Nicklas TA, Hughes SO, Morales M. The benefits of authoritative feeding style: caregiver feeding styles and children's food consumption patterns. Appetite. 2005;44:243–9.
25. Sacco LM, Bentley ME, Carby-Shields K, Borja JB, Goldman BD. Assessment of infant feeding styles among low-income African-American mothers: comparing reported and observed behaviors. Appetite. 2007;49:131–40.
26. Ventura AK, Birch LL. Does parenting affect children's eating and weight status? Int J Behav Nutr Phys Act. 2008;15:5.
27. Fomon SJ, Filmer LJ, Thomas LN, Anderson TA, Nelson SE. Influence of formula concentration on caloric intake and growth of normal infants. Acta Paediatr Scand. 1975;64:172–81.
28. Farrow C, Blissett J. Breast-feeding, maternal feeding practices and mealtime negativity at one year. Appetite. 2006;46:49–56.
29. Wright P, Fawcett J, Crow R. The development of differences in the feeding behavior of bottle-and breast-fed human infants from birth to two months. Behav Process. 1980;5:1–20.

30. Fisher JO, Birch LL, Smiciklas-Wright H, Picciano MF. Breast-feeding through the first year predicts maternal control in feeding and subsequent toddler energy intakes. J Am Diet Assoc. 2000;100(6):641–6.
31. Wright CM, Parkinson KN, Drewett RP. How does maternal and child feeding behavior relate to weight gain and failure to thrive? Data from a prospective birth cohort. Pediatrics. 2006;117(4):1262–9.
32. Burdette HL, Whitaker RC, Hall WC, Daniels SR. Maternal infant-feeding style and children's adiposity at 5 years of age. Arch Pediatr Adolesc Med. 2006;160:513–20.
33. Farrow C, Blissett J. Does maternal control during feeding moderate early infant weight gain? Pediatrics. 2006;118(2):e293–8.
34. Johnson SL, Birch LL. Parents' and children's adiposity and eating style. Pediatrics. 1994;94:653–61.
35. Birch LL, Fisher JO, Grimm-Thomas K, Markey CN, Sawyer R, Johnson S. Confirmatory factor analysis of the Child Feeding Questionnaire: a measure of attitudes, beliefs and practices about feeding and obesity proneness. Appetite. 2001;36:201–10.
36. Taveras EM, Scanlon KS, Birch L, Rifas-Shiman SL, Gillman MW, Rich-Edwards JW. Association of breastfeeding with maternal control of infant feeding at age 1 year. Pediatrics. 2004;114(5):e577–83.
37. Blissett J, Farrow C. Predictors of maternal control of feeding at 1 and 2 years of age. Int J Obes. 2007;31:1520–6.
38. Farrow CV, Blissett J. Controlling feeding practices: cause or consequence of early child weight? Pediatrics. 2008;121(1):2164–9.
39. Brown A, Lee M. Maternal child-feeding style during the weaning period: association with infant weight and maternal eating style. Eat Behav. 2011;12:108–11.
40. Rifas-Shiman SL, Sherry B, Scanlon K, Birch LL, Gillman MW, Taveras EM. Does maternal feeding restriction led to childhood obesity in prospective cohort study? Arch Dis Child. 2011;96:265–9.
41. Ainsworth MDS, Bell SM, Stayton D. Infant-mother attachment. In: Richards MPM, editor. Integration of a child into a social world. Cambridge, England: Cambridge University Press; 1974. p. 99–135.
42. Hirsh-Pasek K, Burchinal M. Mother and caregiver sensitivity over time: predicting language and academic outcomes with variable and person-centered approaches. Merrill Palmer Quart. 2006;52(3):449–85.
43. Black MM, Aboud FE. Responsive feeding is embedded in a theoretical framework of responsive parenting. J Nutr. 2011;141:490–4.
44. Thompson AL, Mendez MA, Borja JB, Sdair LS, Zimmer CR, Bentley ME. Development and validation of the Infant Feeding Style Questionnaire. Appetite. 2009;53:210–21.
45. Worobey J, Lopez M, Hoffman D. Maternal behavior and infant weight gain in the first year. J Nutr Educ Behav. 2009;41(3):169–75.
46. Barnard K. Caregiver/parent–child interaction feeding manual. Seattle, WA: NCAST Publications; 1994.
47. Faith MS, Scanlon KS, Birch LL, Francis LA, Sherry B. Parent-feeding strategies and their relationship to child eating and weight status. Obes Res. 2004;12(11):1711–22.
48. Worobey J, Islas M. Perception and preferences for infant body size by low-income mothers. J Reprod Infant Psychol. 2005;23(4):303–8.
49. Paul IM, Savage JS, Anzman SL, Beiler JS, Marini ME, Stokes JL, et al. Preventing obesity during infancy: a pilot study. Obesity. 2011;19(2):353–61.

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